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Cancer Survival in Scotland: Understanding Social Variations

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ABSTRACT

Large geographical variations in cancer survival are seen across Europe and the UK. Within Scotland there are also large differences between groups of society defined by material deprivation.

The main goal of this thesis is to identify the most important determinants of social variation in cancer survival in Scotland and to assess how these might be addressed in order to reduce inequalities. The underlying purpose is to investigate the usefulness of routine data sources in examining prognosis and patterns of cancer care in the general population. Scotland is ideal for this because of the routine linkage of cancer registry data with all hospital inpatient discharge records.

Chapter 1 of the thesis introduces the statistical methodology, and the measures of deprivation and comorbidity that have been used. Chapter 2 covers the data, definitions and quality issues. Chapter 3 reviews cancer survival in Scotland, including trends over time, and age-, sex- and deprivation-related differences. Chapter 4 explores the concept of avoidable deaths, and compares the methods available for computing this statistic. Six cancers, each with strong evidence of a deprivation gradient in survival in Scotland, were investigated further (breast, colon, rectum, bladder and kidney, and melanoma of the skin), using data for patients diagnosed in 1997. The analyses focus on patient and tumour characteristics, and health care system and treatment factors.

The main findings are that deprived patients have higher comorbidity at diagnosis and appear to present with more advanced tumours. There are wide differences in the treatment offered to affluent and deprived patients, which will be to some extent appropriate because of differences in stage of disease and general health but appear too large to be equitable. Almost half of the excess cancer deaths occurring from these cancers each year, due to differences in survival between deprivation groups, would appear to be avoidable by changes in policy or practice.

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INTRODUCTION

There is extensive information in both the national and international literature describing large variations in cancer survival. Within Scotland, regional and social differences in survival have been reported¹, and similar variations are observed in England and Wales^{2,4}. Survival from many cancers in Scotland is not as high as in comparable European countries^{5,6}. Many possible factors contributing to these inequalities have been individually studied for some cancers, but the relative importance of these factors and the public health implications need to be addressed.

It has long been recognised that the socially disadvantaged have a shorter life expectancy due to the combination of greater incidence of life threatening diseases (including cancer) and then poorer chances of surviving the disease, and these inequalities have widened in recent years⁷. The first reports of socio-economic status being linked to survival time following a diagnosis of cancer date back to the 1950s⁸. Subsequently, socio-economic differences in survival have been reported for many cancers^{9,17} and for most cancers it has been found that the more affluent live longer after a cancer diagnosis than the deprived. Socio-economic differences in cancer survival, if not artefactual, may be related to differences in the extent of disease at time of diagnosis^{15,17}, in the treatment provided^{18,26}, in access to a cancer specialist^{27,30}, or attendance at a specialised cancer hospital³¹ (although evidence on this is conflicting³²), in the biological characteristics of the cancer or in host factors³³. Measures to reduce socio-economic differences in survival depend on our comprehending the complex relations between social factors, individual behaviour, disease processes, and medical interventions, and their combined prognostic significance.

Socio-economic inequalities in cancer survival could in principle be accounted for by three types of explanation: artefactual, random variation in the data and true systematic variation³⁴. Establishing the magnitude of any true systematic variation and the factors involved is, potentially, of great public health importance as this represents the extent to which changes can be made which will reduce the inequalities.

Artefactual explanations for observed differences in cancer survival include data quality, methodological limitations in the estimation of survival causing bias³⁵, and the measurement of deprivation - ideally material deprivation would be measured on an individual basis using information on income, education or occupation. In practice, however, this information is not often available from cancer registries. Random variation is accounted for in statistical analyses. Some of the factors that have been explored in the literature to explain systematic variation in survival between socio-economic groups are now introduced. Each of these has been explicitly considered in the analysis and discussion of cancer survival in Scotland in the subsequent chapters.

Tumour biology

The histological type of malignancy can be an important prognostic factor in cancer survival, because it is associated with aggressiveness of the tumour for many cancers. Differential distribution of histological types of a given cancer between deprivation groups has been seen and may be due to differences in exposure to known risk factors. However, studies adjusting for histological type in survival analyses have generally not found that it accounts for much of the variation in cancer survival between different races³⁶ or deprivation groups³⁷.

Delay in diagnosis and tumour stage at diagnosis

The literature suggests that stage of disease at diagnosis is the most important factor contributing to deprivation-specific differences in cancer patient survival. This has been observed for a number of cancers, and most of the studies suggest that cancer is diagnosed at an advanced stage more often in lower than in higher social classes. Despite these differences, the survival variations by social class have generally persisted even after adjustment for stage^{15,17,38}.

Differences in tumour stage at diagnosis are linked to the speed with which the patient seeks medical advice when experiencing symptoms, the quality of primary diagnosis, the speed of referral to a specialist, and the thoroughness of investigation and diagnosis. The survival advantage conferred by earlier diagnosis may be artificial (lead-time bias): the time of diagnosis is advanced but death is not delayed - that is, treatment does not alter the natural history of the disease^{39,40}.

Quality and timeliness of treatment

Differences in treatment by deprivation group have not been widely studied. Studies in the USA have found differences in treatment for breast cancer by race, as a surrogate for deprivation⁴¹, and lung cancer by whether or not patients had private medical insurance⁴². Differences in cancer survival based on the quality of treatment have been estimated by looking at survival in specialist hospitals³¹ and treated by cancer specialists^{27,30}, but these differences have not been investigated in the context of deprivation. The choice of treatment will be influenced by clinical judgement based on stage at diagnosis and other tumour characteristics.

Comorbidity and host response

Host factors include both biological factors such as co-morbidity, and psychosocial factors such as health behaviour. Berg *et al.*⁴³ propose a hypothesis that poor nutritional status, general health and immunological status (related to alcoholism) of deprived social groups leads to lower survival from cancer. Co-morbid conditions experienced by cancer patients may vary substantially between populations. They could in turn affect survival by presenting an additional source of risk of death, making it less likely that a patient will be offered curative treatment or, if it is offered, less likely that the patient will be able to withstand the effects of the treatment itself.

The government is committed to reducing mortality from cancer^{44,47} and has acknowledged that there are inequalities in cancer survival. Although many studies to investigate variations in cancer survival exist, there is no comprehensive investigation of the relative importance of all factors known to affect survival and their relationship with deprivation. Differences in tumour biology and host response between deprivation groups need to be identified and quantified but they are difficult to change. If delay in diagnosis and the quality and timeliness of treatment could be shown to be important influences on socio-economic differences in survival, however, that would be of great public health relevance. These factors can be influenced by improvements of health care systems and health information, which would in turn reduce the socio-economic gradient in survival.

The aims of this thesis

The main aim of this PhD thesis was to identify the most important determinants of social variations in cancer survival in Scotland and to assess how these factors should be addressed in order to reduce inequalities in Scotland. The underlying purpose of the thesis was to investigate the use of routine data sources to look at prognosis and the patterns of cancer care in population-based cohorts of cancer patients. Routine data sources, if suitably reliable, are very valuable. They allow "up-to-date" analyses, can be updated regularly with comparative ease, and they are not resource intensive. Results of retrospective audits are often published many years after the date of collection, by which time case-mix and treatment practice may have substantially changed, and this reduces their usefulness. Scotland is the ideal place to investigate routine data sources, due to the central resource of data collected from all hospital computer systems and the linkage of these data to form patient care histories.

Chapters 1 and 2 of the thesis discuss the methodology and materials used. Chapter 3 presents a brief overview of survival from cancer in Scotland including trends over time, and age-, sex-, and deprivation-related differences. Chapter 4 looks at the concept of avoidable deaths and compares the methodology available for computing this statistic. The research is then focused on six cancers (Chapters 5-8) to investigate differences in tumour biology, delay in diagnosis, tumour stage at diagnosis, the quality and timeliness of treatment, and co-morbidity. These in-depth analyses cover cancers of the breast, colon, rectum, kidney and bladder, and melanoma of the skin. These are all common malignancies with substantial mortality, and for each of them there is strong evidence of a significant deprivation gradient in survival in Scotland. Detailed discussion is included in each of these chapters. There is also a general discussion at the end of the thesis containing broad comments and an overall interpretation of the results.

METHODOLOGY

Cancer survival rates

The simplest estimate of survival is *observed survival*, which is the probability that a person with a given disease will be alive at a specified time-point t_j after diagnosis. It does not take cause of death into account; however, survival of cancer patients depends both on the risk of death due to the cancer, and on the background risk of death in the general population which the cancer patient is a member. The risk of death due to the cancer tends to decline with increasing time since diagnosis, while the background risk from other causes of death will increase as the surviving patients get older. It is therefore important to separate the background risk of death and the risk of death from the cancer. Observed survival is always likely to be lower in older patients, because they are at greater risk of dying from other causes. This makes it difficult to compare survival between age groups or between populations with different age distributions. *Cause-specific* and *relative survival* attempt to overcome this problem; they can be thought of as a measure of *net* survival expectation after contracting cancer, or the probability of survival from cancer *in the absence of other causes of death*.

Observed (or crude) survival

Observed survival and its standard error are calculated by,

$$S_i = \prod_{j=1}^i \left(1 - \frac{d_j}{n_j}\right), \quad se\{S_i\} = S_i \left\{ \sum_{j=1}^i \frac{d_j}{n_j(n_j - d_j)} \right\}^{\frac{1}{2}}$$

where

t_j = j th observed time of death

- $1 - \frac{d_j}{n_j}$ = Conditional probability of surviving to t_j , having survived to just before t_j
 d_j = Number of deaths occurring at time-point t_j
 n_j = Number of patients alive just before time t_j (i.e. including deaths at t_j but excluding patients censored before t_j)

Censored patients are those whose vital status is not known after a given time-point. For example, in this thesis patients who are still alive on 31st December 1999 are censored on that date because, at the time the data extract was taken, the death data were not complete on the cancer registration file after that date. Similarly, patients who have emigrated during the period of follow-up are censored on their date of emigration.

Crude survival is a useful measure: it gives the "real" survival of the patients diagnosed with cancer.

Cause-specific (or net or corrected) survival

Cause-specific survival is calculated using the same methodology as observed survival, with the cause of death from the death certificate used to attribute the death either to the cancer or to other causes. Deaths from causes other than cancer are censored in the survival analysis to give a cause-specific survival rate. This method is used as standard in the clinical trials setting. However, in the population-based setting, problems arise particularly for patients with long follow-up. Firstly, it is not always clear which deaths should be considered as attributable to the cancer of interest (e.g. suicide, surgical complications, a second cancer). Secondly, the cause of death information is not always available, accurate and complete. Since the 1990s, the completeness of death certificate information in Scotland has been high (99% of deaths have at least one cause of death recorded). The most recent study of the accuracy of death certificates in Scotland was for death certificates completed from 1975-1977⁴⁸; at that time, the death certificate information was found to be highly unreliable as a source of diagnostic data. This information is believed to be much more reliable now, but there is no recent evidence on this point.

For each cancer, Appendix 1.1 shows the causes of death which were deemed to be cause-specific for the purposes of this thesis. The aggregation of the deaths defined as cause-

specific for each cancer gives the cause-specific deaths for 'all malignant neoplasms'. The list is not necessarily exhaustive or definitive. If causes which should be attributed to the cancer of diagnosis are excluded, cause-specific survival will over-estimate 'net' survival; conversely, if too many causes of death are included, cause-specific survival will underestimate 'net' survival.

There may be differences between areas or countries in the conventions used for completing death certificates, so cause-specific survival is likely to be most useful for comparing sub-groups within a country, for example between areas or deprivation groups, as in this thesis. The use of cause-specific methods to assess socio-economic differences in survival of cancer patients depends partly on the assumption that the accuracy of death information does not vary by social class⁴⁹. Although one study in Scotland suggested that this assumption may not be valid, it was based on a relatively small and selected series of autopsy cases⁵⁰.

Due to the uncertainty of the accuracy of the death certificates and the subjectivity of the definition of "cause-specific", this method is used only in an exploratory manner in this thesis.

Relative survival

Relative survival is the usual method of estimating net survival in population-based studies. It is the ratio of observed survival compared to the survival that would have been expected in the cohort of patients if they had been subject only to the mortality rates of the background population (expected survival). At time-point t_i , relative survival is calculated by

$$R_i = \frac{S_i}{E_i}$$

S_i is the observed survival as described earlier; E_i is the expected survival, that is the average expected survival in a comparable group of the general population with respect to the main factors affecting survival (e.g. age and sex). The expected probabilities are obtained from life tables for Scotland (described later) allowing the calculation of the expected probability of survival at each single year of age at death.

While relative survival is expected to give values that are more comparable between different populations, it should be borne in mind that it is unlikely to represent the true 'net' survival completely. For example, it is possible that patients diagnosed with cancer are more likely to die from other causes than the general population and hence relative survival may still be an overestimate of 'net' survival.

Two early methods by Ederer *et al.*⁵¹ for calculating relative survival are documented. With the first method (Ederer I), the probability of surviving t years after diagnosis is obtained from relevant life tables for each individual in the study cohort; the expected number of survivors is obtained by dividing the sum of these probabilities by the initial size of the cohort. This method was then enhanced (Ederer II), with the probability of survival in each "actuarial" interval being estimated at the beginning of the interval for each individual still at risk at that time. Again, the probabilities are summed to estimate the expected number of survivors in the interval. The relative survival at t years after diagnosis is the product of the ratios of observed to expected actuarial survival within each interval up to t .

However, even with this enhanced method there is a problem with heterogeneity within the study cohort, of covariates (e.g. age) which affect survival, and to changes in their distribution as the study cohort is depleted by death and censoring⁵². For example, in the longterm, the net survival will be dominated by the net survival of the group with the longest life expectancy (usually the youngest), and for many cancers net survival is better for those diagnosed at a younger age. Hakulinen *et al.*⁵³ suggested changing the calculation so the expected survival is updated at each event (death) using the demographic information for the case at that point in time, hence correcting for heterogeneity in expected survival and patient withdrawal (i.e. young patients may be more likely to withstand treatment; young patients may be less likely to die from an unrelated condition; young patients may be more likely to emigrate from the cancer registry area).

Estève *et al.*⁵⁴ were still concerned that this method may over-estimate long term net survival in cohorts with heterogeneous life expectancies, because the expected survival relies only on the initial composition of the cohort and on the potential follow-up times. They, therefore, proposed modelling the data using a full likelihood approach based on individual-level data. With this method the death rate from cancer, in each of a series of (pre-defined) time intervals since diagnosis, is estimated from the survival times of individual patients. The

background mortality rate within the interval is assumed to be constant. The net mortality rate in each time interval is estimated using an iterative procedure to maximise the likelihood of the parameters and the net mortality rates, given the observed data. Simplistically, this method consists of subtracting the number of expected deaths from the observed deaths in each interval and inferring the excess mortality rate from this adjusted number.

Detailed methodology for the two approaches are not repeated here, as they can be found in the references^{53,54}.

Computer packages for calculating relative survival rates

Observed and cause-specific survival can easily be calculated using any statistical analysis package. However, the calculation of relative survival involves quite complicated programming. A stand-alone computer package, *snrv3*, is available to compute the Ederer and Hakulinen estimates⁵⁵. Also available is a STATA algorithm, *strel2*, based on the relative survival approach outlined by Estève *et al.*

The *snrv3* programme analyses the data at every event, so there are no input decisions to be made by the user. With the *strel2* algorithm however, the analysis is performed at time points (known as breaks) decided by the user. The choice of these time points is important because the excess hazard is assumed constant within each interval, however, when there are many deaths the excess hazard will in fact change rapidly. After testing a selection of options for these break points on different types of survival data, the following guidelines seem appropriate for users of the algorithm (see box).

The estimates produced by the *snrv3* package and the *strel2* algorithm are quite similar for analyses containing at least 50 patients. For analyses including fewer than 50 cases, the estimates are often not comparable. The estimates produced by the *strel2* algorithm are generally (85%) somewhat lower than those produced by the *snrv3* package.

In this thesis, both crude and relative survival methodologies have been used. In Chapter 3, the Estève relative survival method has been used to allow comparison with published work. In Chapter 4, where the relative survival rates are modelled, the Hakulinen method has been used as it was not possible (at the time of analysis) to model the estimates produced by the

Estève method. For Chapters 5-8, crude survival estimates are used as only short-term survival (2-years) is considered and complex modelling is performed.

Box 1.1: Comparison of the *surv3* package and *strel2* survival estimates

	Patients available for analysis	
	Up to fifty	More than fifty
If one-year survival is expected to exceed 60%	<p>For the <i>strel2</i> algorithm: Use no more than three intervals in the first year, and no more than yearly intervals thereafter (ensure there are not more intervals than deaths in subsequent years)</p> <p>These estimates can vary significantly from <i>surv3</i> estimates</p> <p>Recommended <i>strel2</i> code 0[0.33]1[1]5</p>	<p>For the <i>strel2</i> algorithm: Not sensitive to number of breaks as long as at least four-monthly intervals are used in the first year, and at least yearly intervals thereafter</p> <p>Around 93% of estimates are within two percent of the corresponding <i>surv3</i> estimates</p> <p>Recommended <i>strel2</i> code 0[0.25]1[0.5]5</p>
If one-year survival is expected to be less than 60%	<p>For the <i>strel2</i> algorithm: Use monthly intervals in the first year if possible (ensure that there are not more intervals than deaths). Use at least yearly intervals thereafter</p> <p>These estimates can vary significantly from <i>surv3</i> estimates</p> <p>Recommended <i>strel2</i> code 0[0.083]1[0.5]5</p>	<p>For the <i>strel2</i> algorithm: Not sensitive to number of breaks as long as at least two-monthly intervals are used in the first year, and at least yearly intervals thereafter</p> <p>Around 85% of estimates are within two percent of the corresponding <i>surv3</i> estimates</p> <p>Recommended <i>strel2</i> code 0[0.167]1[0.5]5</p>

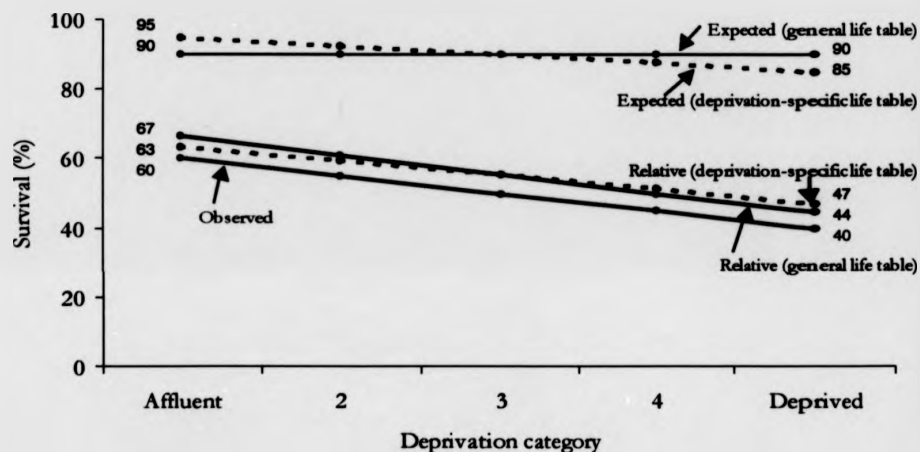
Life tables

A life table is an age-specific mortality table constructed using numbers of deaths and population estimates. When the number of deaths is small it is appropriate to smooth the constructed table, which can be done using several methodologies including a relational life table approach⁵⁶. Background mortality varies by sex, time period, region and deprivation group, so comparisons of survival between groups need to take account of this by using appropriate life tables. For example, when comparing survival between deprivation groups, the general life table will tend to over-adjust the background mortality in the affluent group and under-adjust the background mortality in the deprived group, so that the differences in excess cancer mortality between affluent and deprived look wider than they actually are.

Figure 1.1 illustrates this point with a published hypothetical example: when a single life table is used (i.e. the expected survival is constant at 90% across all deprivation groups) the

difference in relative survival between the most affluent and deprived groups is 23% (i.e. 60/90 - 40/90), and when deprivation-specific life tables are used (i.e. the expected survival ranges from 95% to 85%) the gap in relative survival between the most affluent and deprived groups drops to 16%⁴.

Figure 1.1: Difference in relative survival estimates when using deprivation-specific compared to general life tables



Source: Coleman *et al.*⁴

This effect can be demonstrated in Scottish data. The difference in survival between deprivation groups is over-emphasised for all cancers when a general life table is used, with a large variation in the differences for some cancers (Table 1.1). It is worth noting that when results for all deprivation groups are shown as a combined estimate, the results are similar whichever life table is used (data not shown).

Deprivation-specific life tables for Scotland had to be specially constructed for the analyses in this thesis. Numbers of deaths by deprivation category were calculated using the postcode information for each death (supplied by the Scottish General Registrars Office (GROS)). Population estimates by postcode sector were available from the 1991 census, and adjustments for known undercount³⁷ were obtained from the Manchester University Census website (MIMAS) to attempt to account for deprivation-related bias in the census

coverage. The resulting mortality rates were in five-year age bands up to age 85+. These were then smoothed and extrapolated to give single-year-of-age estimates for ages 0-99 using the relational life table approach, using excel macros kindly supplied by Mr A Sloggett, LSHTM (personal communication). Published life tables for Scotland were used as the standard against which to smooth the deprivation-specific mortality rates.

Table 1.1: Comparison of five-year relative survival rates by deprivation group when using general and deprivation-specific life tables: patients aged 15-99 diagnosed in Scotland during 1991-95

Cancer	General life table			Deprivation-specific life tables		
	Affluent	Deprived	Difference	Affluent	Deprived	Difference
Oral cavity	56.8	43.0	13.9	55.4	44.4	11.0
Oesophagus	6.5	6.4	0.1	6.3	6.7	-0.4
Stomach	10.0	9.7	0.3	9.7	10.0	-0.3
Colon	40.9	35.1	5.9	40.0	36.2	3.8
Rectum	41.3	33.5	7.8	40.2	34.7	5.5
Pancreas	2.8	2.0	0.8	2.7	2.1	0.7
Larynx	70.9	56.8	14.1	68.7	58.9	9.8
Lung	6.3	4.9	1.4	6.1	5.1	1.0
Malignant melanoma	82.2	72.3	9.9	81.1	73.7	7.4
Breast	71.3	61.5	9.8	70.5	62.5	8.0
Cervix uteri	66.9	60.9	6.0	66.3	61.7	4.6
Body of the uterus	74.6	69.1	5.5	73.5	70.5	3.1
Ovary	30.8	27.6	3.2	30.4	28.1	2.3
Prostate	45.3	37.4	7.9	43.0	39.5	3.6
Testis	93.5	85.9	7.6	93.1	86.5	6.6
Bladder	67.7	56.4	11.3	65.5	58.7	6.8
Kidney	40.1	33.7	6.3	39.1	34.8	4.3
Brain and other CNS	14.7	12.5	2.2	14.5	12.7	1.9
Thyroid	78.1	70.0	8.1	77.0	71.5	5.5
Non-Hodgkin lymphoma	49.7	40.7	9.0	48.6	41.9	6.8
Hodgkin's disease	79.8	70.5	9.3	78.9	71.4	7.5
Multiple myeloma	19.9	18.1	1.8	19.3	18.7	0.6
Leukaemia	28.8	22.9	5.9	28.2	23.6	4.6

Age standardisation of age-specific survival rates

Both relative and cause-specific survival estimates account for age-specific differences in background mortality, but not for the fact that survival after a diagnosis of cancer also differs with age, and is in general likely to be worse in older patients. In order to compare survival in cancer patient populations with different age structures, survival estimates can be age-standardised by calculating the survival in a 'standard population' of fixed age/sex distribution. The *standardised survival rate* is the sum of the age- and sex-specific survival rates multiplied by the corresponding sex- and age-group weight for the standard population. The following steps are used to standardise for age and sex:

1. Specify a standard age and sex distribution by calculating the proportion of the standard population falling within each age and sex group, P_{ij} .
2. Calculate survival within each age and sex group in the population of interest, S_{ij} .
3. Calculate the standardised survival rate (A) as a weighted sum of the age- and sex-specific survival estimates, S_{ij} , with weights given by the standard population proportions, P_{ij} .

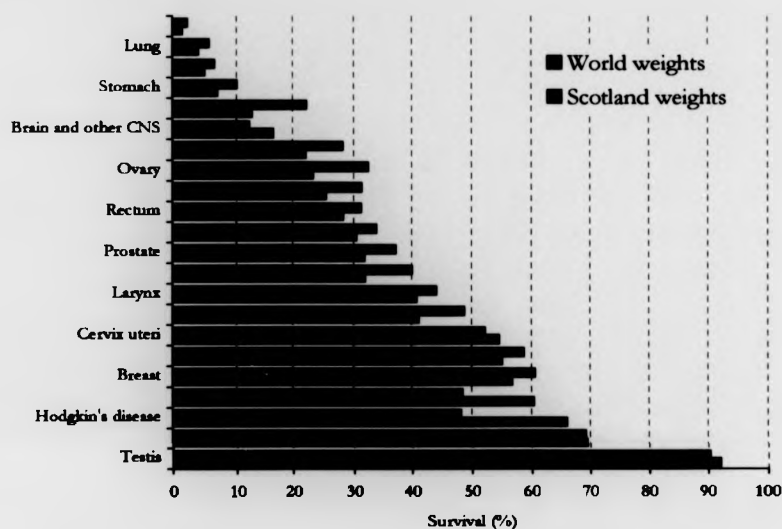
$$A = \sum_{i,j} P_{ij} S_{ij}$$

The weights used for age-standardisation can be based on the age-specific incidence pattern of each cancer site in the dataset being analysed (as in 1 above). A set of standard weights based on the pattern of cancer in the world (analogous to the World Standard Population used for age-standardised incidence) has also been published⁵⁸. The World Standard Cancer Patient Population has a greater proportion of younger patients than in Scotland so the standardised survival rate is weighted towards that of younger patients. For this reason, world-standardised results for Scotland will often be higher than unstandardised results.

Standardisation with Scottish cancer patient population weights and world standard cancer patient population weights produces very different standardised survival estimates (Figure 1.2), highlighting the importance of using the set of same weights when comparing different survival estimates. Care must be taken when using the world standard cancer patient population weights if age-specific estimates with a substantial weight are based on a small number of cases (e.g. at young ages). This can result in misleading estimates, as observed for Hodgkin's disease (world standardised rate is 14% lower), thyroid cancer (10% lower), multiple myeloma (10% higher) and ovarian cancer (7% higher) in the analyses shown.

The choice of age bands used to construct the standardised estimate can also have a subtle effect on the standardised estimates, particularly when small numbers of cases are involved in analyses. If possible, the age bands should be consistent across the analyses being compared. Age-standardisation requires a sufficient number of cases in each age group to compute a survival rate.

Figure 1.2: Age-standardised five-year relative survival estimates, comparison of Scottish and World standard cancer population weights: patients aged 15-99 diagnosed in Scotland during 1991-95



The World Standard Cancer Patient Population (see Appendix 1.2) is used to estimate age-standardised survival rates in Chapter 3 of this thesis. It specifies a separate set of weights for each cancer. For cancers where no world standard weights were available (brain and other CNS, thyroid), the 'all cancers' weights were used. Using a different set of weights for each cancer means that age-standardised survival rates can be compared across areas (or between deprivation categories, over time, etc.) for a particular cancer, but cannot so readily be compared between cancers.

Multivariate analysis of survival data

An alternative approach to standardisation is to estimate *adjusted* survival rates. This approach is appropriate when a comparison is to be made between several populations for which data on individual patients are available. It involves fitting a regression model with 'adjustment' factors (e.g. age and sex) included as independent variables. This produces estimates for each population that are 'adjusted' for the factors included. Adjusted estimates can be thought of as 'averaged' over the factors included in the model. For example, age-,

sex- and deprivation-adjusted hazard ratios for each health board in Scotland correspond to estimates based on patients with the average distribution of age, sex and deprivation across Scotland. Two multivariate methods are considered in this thesis: Cox proportional hazards regression analyses and generalised linear modelling.

Cox proportional hazards regression

This method was first introduced by Cox³⁹ and is the most commonly used regression model for survival data. It is used to study the relationship between time to an event and a set of independent variables, and depends only on the ranks of the survival times. The time until an event occurs can be censored, i.e. the event of interest need not occur for all cases. The dependent variable is the length of time a patient survives (for those who are still alive the dependent variable is the time until censoring). The independent variables can be the age of the patient, hospital of treatment, stage of disease at diagnosis, treatment given, etc. Different selection (e.g. forward or backward selection) methods can be used to identify the subset of independent variables that are related to the dependent variable.

Cox proportional hazards regression is described in detail in most epidemiological text books. In brief, if $Z_i(t)$ is the vector of covariates for the i th individual at time t , the model assumes that the hazard for a subject is of the form

$$\lambda(t;Z_i) = \lambda_0(t) \cdot r_i(t),$$

where $r_i(t) = e^{\beta \cdot Z_i(t)}$ is referred to as the risk score for the i th subject, β is a vector of regression parameters and $\lambda_0(t)$ is an arbitrary and unspecified baseline hazard function. The exponential function guarantees that λ is positive for any β .

Assuming that a death has occurred at time t^* , then conditional on this death occurring, the likelihood that it would be subject i rather than some other subject is

$$L_i(\beta) = \frac{\lambda_0(t^*) \cdot r_i(t^*)}{\sum_j Y_j(t^*) \lambda_0(t^*) \cdot r_j(t^*)} = \frac{r_i(t^*)}{\sum_j Y_j(t^*) \cdot r_j(t^*)}$$

The partial likelihood is the product of the terms over all death times $L(\beta) = \prod L_i(\beta)$. Maximisation of $\log(L(\beta))$ gives an estimate for β without the need to estimate the nuisance parameter $\lambda_0(t)$. An estimator of the covariance matrix is given by the inverse of the second derivative matrix.

Cox proportional hazards regression modelling is available in most statistical computer packages. The STATA statistical package is used to model the data for Chapters 5-8 of this thesis.

Model checking and validation

The adequacy of the model can be investigated using Cox-Snell residuals which are obtained from the cumulative hazard ($\hat{\tau}$) for each individual. These values are taken as the 'survival times' and analysed in a Kaplan-Meier analysis to obtain the values of $S(\hat{\tau})$. A plot of the $\log(-\log S(\hat{\tau}))$ versus $\log(\hat{\tau})$ should give a straight line with slope 1 and intercept 0, which implies that the residuals can be assumed to come from a unit exponential distribution which, in turn, implies a good model fit.

The assumption of proportional hazards can be assessed initially by checking the survival curves for each of the factors in the analysis to check they do not cross or diverge considerably. Also, the log cumulative hazard can be plotted against time since diagnosis to look for departures from parallelism. However, the interpretation of these plots is subjective, and proportionality can be examined formally using time-dependent modelling. Each level of a factor with a time interaction can be compared to the baseline. The interaction term is added to the full model so that time-dependency can be checked after allowing for the effects of the other explanatory variables in the model. For each model, the other factors are assumed to be independent of time. The p-value for the Wald statistic will be non-significant (i.e. no changing risk ratio of death over time) if the proportionality assumption is met. In STATA proportionality can be examined using the scaled Schoenfeld residuals command.

Generalised linear modelling

Hakulinen and Tenkanen⁶⁰ outlined an approach to model relative survival using generalised linear models (GLMs). The survival data are grouped and the total mortality (μ) in each interval is modelled using a binomial distribution. The model is based on the sum of the known baseline mortality (expected mortality), μ^* , and the excess mortality due to a diagnosis of cancer, v . Such that,

$$\mu_{rsj} = \mu^*_{rs} + v_{rsj}$$

where j = follow-up interval and r, i, s are stratification variables such as age, sex and stage.

The baseline mortality in this approach is allowed to vary with each stratification variable, which can be categorical or continuous. Interaction terms can be added to obtain an acceptable fit to the data if non-proportional excess hazards are suspected.

The excess mortality is assumed to be a multiplicative function of the covariates, such that

$$v_{rsj} = \exp(\beta_r + \beta_i + \beta_s + \beta_j)$$

This method is based on aggregated data, so it is not as powerful as the Cox proportional hazards regression modelling, however, its advantage is that it takes underlying mortality into account. The problem of heterogeneous withdrawal can be minimised by careful selection of stratification variables.

Generalised linear modelling of relative survival estimates can be programmed in SAS or STATA. Programs written in SAS have been used in Chapter 4 of this thesis.

Model checking and validation

One of the advantages of this method is that the theoretical basis of generalised linear models can be utilised for regression diagnostics and assessment of goodness of fit.

The deviance statistic is used to assess the goodness of fit, and a good fit is assumed if it follows a chi-square distribution with degrees of freedom equal to the number of residual degrees of freedom of the model (number of observations minus number of estimated parameters). The residuals and influence statistics are studied for evidence of lack of fit.

Missing data

Three approaches have been used in this thesis to investigate problems of missing values for breast cancer. Firstly, and most simply, cases with missing data are excluded from the analysis under the assumption that these patients are representative of the whole population and are not a biased group. Secondly, an additional category for "unknown" is included for each variable, although this has been shown to lead to biased estimates of odds ratios⁶¹. Thirdly, the missing values have been imputed. Imputation relies on the data being missing completely at random (MCAR) or missing at random (MAR; the probability that data are missing varies only with respect to specified categorical variables e.g. age group).

The missing data for stage (for example) can be imputed ad-hoc, based on knowledge of the proportions of known stage within different sub-groups (e.g. age group and treatment group)^{61,62} or multiple imputation can be used, where the data are repeatedly modelled and all the values (both known and unknown) replaced based on the model parameter estimates⁶³. The resulting m versions of the complete data are then analysed in the standard manner and the results combined to produce confidence intervals that incorporate missing-data uncertainty. An algorithm called *hotdeck* is available in STATA which uses the approximate Bayesian bootstrap multiple imputation method of Rubin and Schenker (1991)⁶⁴. The missing values are imputed stochastically i.e. the missing values in each specified sub-group (e.g. age group) are sampled with replacement from the complete data in the same sub-group, and the missing values are sampled at random (again with replacement) from the bootstrap sample. This is the imputation approach taken in this thesis. The sub-groups for stratification have been selected using logistic regression where the outcome (for the variable of interest) was missing or non-missing.

Measures of deprivation

Deprivation is a concept that overlaps but is not identical to, that of poverty. Absolute poverty can be defined as the absence of the minimum resources for physical survival,

whereas relative poverty relates to the standards of living in a particular society. Deprivation includes material and social deprivation and these are often discussed interchangeably in the literature. There is no generally agreed definition of deprivation. Ideally, socio-economic status (or material deprivation) would be measured on an individual basis using information on income, education or occupation. In practice, however, this information is rarely available from cancer registries. Instead, deprivation for individuals is estimated from aggregate data derived from the census.

Census area-based deprivation indices

These are used to estimate deprivation of individual cancer patients in small census areas e.g. census enumeration districts (approx. 400 households) for England and Wales, or postcode sectors (approx. 2 000 households) for Scotland. The smallest area base available should be used to minimise misclassification; however, the smaller the geographical area, the more it will be influenced by the arbitrariness of the boundaries (e.g. postcode sectors are allocated to ease postal deliveries, not because the residents have similar social features). In Scotland, postcode-sector is the smallest area base available, and the deprivation score for each patient is assigned on the basis of his or her postcode-sector of residence at the time of diagnosis.

The problems with using small-area deprivation indices are well documented⁴⁵. The most important is that they rely on the census, so information is only available at 10-year intervals (e.g. 1971, 1981, 1991, 2001), during which time the level of deprivation within an area may change. This can be investigated with the Scottish data. There are 886 postcode-sectors in Scotland to which we can assign a Carstairs deprivation score (described later) based on either the 1981 or 1991 census. If we compare the seven-level deprivation categories that postcode-sectors are assigned to, based on the two scores, many remain in the same deprivation category (59%), a third shift up or down by one category (36%) and 43 (5%) of the postcode sectors shift by more than one category (Table 1.2).

A second concern is that the census variables chosen to represent material deprivation may not be realistic. For example, some indices use car ownership as an indicator of affluence, but the use of a car in rural areas may be essential, so rural poverty may not be properly measured by this component of deprivation, and the resulting scores would be more likely to be 'true' indicators of deprivation in urban than rural areas.

Table 1.2: Carstairs score (seven levels) for postcode-sectors in Scotland: a comparison of the agreement between the 1981 and 1991 scores¹

1981	1991						
	Affluent	C2	C3	C4	C5	C6	Deprived
Affluent	43	11					
C2	21	85	31				
C3		37	139	35			
C4			58	123	21		
C5				41	55	14	
C6					25	45	5
Deprived						18	35

¹ Shaded areas are number of postcode sectors that changed by more than two levels between 1981 and 1991

Another problem is that the defined areas may not contain homogenous populations (ecological fallacy: 'poor' areas contain some affluent people, 'rich' areas contain some poor people). It has been estimated that 55% of the most deprived individuals in England and Wales live outside the 20% of areas that are most deprived⁶⁶, and areas containing a mixture of deprived and less deprived households will be likely to get middle-ranking deprivation scores. The ecological fallacy is a particular problem with the elderly, because although the level of deprivation of a given area may change, old people tend to move less frequently than younger people, and may therefore be mis-classified more often (Table 1.3).

Table 1.3: Correlation of mortality with deprivation, Scotland, 1979-83

Census variable	Townsend ages 0-64	Carstairs ages 0-64	Carstairs ages 65+
Deprivation ¹	0.62	0.75	0.53
Unemployed	0.61	0.70	0.51
Overcrowded housing	0.55	0.64	0.49
Lacking car	0.61	0.74	0.50
Head of household in low social class	0.57	0.62	0.39
Not in owner-occupier housing	0.39	-	-

Source: Hanni and Fujimoto⁶⁷

¹ Definitions differ

The census does contain a social class variable, indicating the proportion of households of which the head of household is in social class IV and V, based on his or her occupation. This variable was assigned for only a 10% sample of the census, and may therefore be based on very few cases at the small-area level. This is less of a problem in Scotland, where the smallest area base is the postcode sector, which contains many more residents than the enumeration districts used in England and Wales.

However, despite these potential problems, deprivation indices are often the "best" estimate of deprivation that can be gained without actually contacting individuals with a questionnaire. Although some work has been performed on deprivation using data from the 1971 census, most of the important work follows from the improved geographic base provided by the 1981 census⁶⁸ and the more consistent use of postcodes as a basis for determining the area of residence in routine statistical records systems. The two most widely used health-related deprivation indices for cancer analyses are the Carstairs index⁶⁹ and the Townsend index⁷⁰, both developed to represent material deprivation.

Carstairs Index

This index is a combination of census information on household overcrowding, male unemployment, low social class and car ownership. Percentage values for each small area (e.g. census enumeration district or postcode sector) are standardised by subtraction of the mean value for all small areas in Great Britain and division of the result by the population standard deviation. The standardised scores for each of the four census variables are then summed into a single score for each small area, and these deprivation scores are then divided into percentiles (e.g. quintiles), ranging from very high to very low deprivation.

Townsend Index

This index is calculated in the same way as the Carstairs index but using census information on household overcrowding, male unemployment, car ownership and housing tenure (i.e. percentage of households not in owner-occupied accommodation).

Analyses using the Carstairs and Townsend indices give very similar results⁷¹, and both correlate reasonably well with mortality in Scotland, particularly in the younger age groups (Table 1.3). The housing tenure variable does not correlate well for Scottish data because renting is (or was until recently) much more common in Scotland and was not related to wealth. The Carstairs index is used as the measure of deprivation in this thesis, because it was developed for Scottish data and is widely used in Scottish health statistics. It better represents material deprivation in Scotland because it does not include the housing tenure variable, and the problems with the social class variable are minimised by the larger size of the Scottish census areas compared to those in England and Wales. Problems of mis-

classification will tend to dilute rather than enhance any deprivation gradient observed, so true differences are less likely to be picked up but erroneous differences are unlikely to occur

Measuring comorbidity

Comorbidity is an important prognostic indicator for cancer patients, but it presents the analytic challenge of being multi-dimensional. Several scoring systems for prospective analyses have been proposed, with completion of a form or chart by the clinician. Measurements of co-morbidity from routine data sources have had mixed success.

The most widely used comorbidity measure in epidemiological research is the Charlson index⁷², because the information for the index (originally designed for a chart setting) can be extracted from clinically coded (e.g. ICD-9) databases. However, the correlation between the data derived in the two different ways (chart versus database) has been shown to be quite low (0.36-0.47)⁷³. The Charlson index comprises a list of 19 diseases (certain of them representing two degrees of severity of the same condition) with different weights attached (from 1, least severe, to 6, most severe) (see Appendix 1.3). Additional points can be added for increasing age. The sum of these points (weights) can then be collapsed in to four ordinal categories: 0, 1-2, 3-4, 5+. Four of the disease items relate to cancer and, for the study of cancer patients, these are generally excluded from the score, resulting in a shorter range of scores. A potential limitation in the cancer setting is that the index ignores several co-morbidities that may be relevant to treatment of cancer patients, such as haematopoietic disorders (other than malignancies), polyneuropathy or moderate renal dysfunction⁷³. However, a review of the main comorbidity indices found the Charlson index to have the best predictive power for survival⁷⁴. For the purposes of this thesis, the score was compiled based on presence of the non-cancer diseases in the 2 years before the diagnosis of the cancer of interest, and the score defined as 0, 1-2, 3+ points.

In Scotland, another comorbidity score has been compiled⁷⁵, based on the presence of seven conditions in the 2 years before to 1 month after the diagnosis of the cancer of interest. These include diabetes (ICD-9 code: 250), hypertension (401-405), ischaemic heart disease (410-414), other heart disease (390-400, 406-409, 415-429), cerebrovascular disease (430-438), respiratory disease (490-496) and arthritis (714, 715, 719). The co-morbidity score

was then defined as: 0=no admissions, 1=only admitted for one condition (no matter how often), and 2=admitted for more than one condition.

Other major comorbidity indexes include the ICED, CIRS, and Kaplan-Feinstein indices, which are all disease severity indices that cannot be implemented with routine data. The association of these indices, and the Charlson index, with length of hospitalisation or rate of hospitalisation has been studied, with contrasting results⁷⁴.

For this thesis the Charlton and Scottish indices along with a hospitalisation measure of comorbidity have been considered. The hospital measure was the cumulative time (bed-days) spent as a hospital inpatient in a defined time period prior to the cancer diagnosis; the bed-days for each set of patients studied were split into ordinal categories based on percentiles. The bed-days method was tested on five different sets of patients: all the patients included in in-depth analyses in Chapters 5-8 combined, all colorectal cancer patients diagnosed 1986-96 within a restricted age range, colorectal cancer patients diagnosed in 1997 (to look at adjustment for tumour stage), all patients with a first inpatient diagnosis of diabetes 1986-96, and all patients with a first inpatient diagnosis of rheumatoid arthritis 1986-96. For each set of patients, increasing bed days was increasingly predictive of death within two years of diagnosis, after adjustment for age and sex (Table 1.4). Restricting the analysis to exclude cancer-related bed-days, and applying a time limit (e.g. only inpatient stays in the two years preceding the cancer diagnosis) did not change the predictive power of the score. The weaker effect of comorbidity in the cancer patient than in the diabetes and rheumatoid arthritis patient analyses may be because of the complex relationship between comorbidity and cancer morbidity. The number of bed-days in each centile varied for each analysis.

For colorectal cancer patients diagnosed in 1997, the relationship between bed-days in the previous two years and mortality within two years of diagnosis of the cancer, was still seen after adjusting for age, sex and stage. The adjusted survival curves are plotted in Figure 1.3, along with similar curves for the Charlton and Scottish comorbidity indexes. Additionally, all three measures were independently predictive of survival if included together in a multivariate model (data not shown).

Table 1.4: Risk of death according to number of days spent in hospital preceding diagnosis of the condition of interest, adjusted for age and sex: patients diagnosed in Scotland, selected conditions and time periods

Bed-days percentile	Patients diagnosed with breast, colorectal, bladder and kidney cancer and melanoma in 1997			Colorectal 1986-96, ages 60-69	Colorectal, 1997 ²	Diabetes 1986-96	Rheumatoid arthritis 1986-96
	All preceding bed-days	All preceding non-cancer ¹ bed-days	Preceding bed-days within 2 years	Preceding bed-days within 2 years	Preceding bed-days within 2 years	Preceding bed-days within 2 years	Preceding bed-days within 2 years
25 th	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50 th	0.94	0.97	0.93	0.65 ***	1.13	1.25 ***	0.76 ***
75 th	1.03	0.97	1.10 *	0.82 **	1.06	2.66 ***	1.38 ***
90 th	1.19 **	1.21 ***	1.21 **	1.33 ***	1.18 *	4.13 ***	2.38 ***
95 th	1.71 ***	1.65 ***	1.77 ***	2.05 ***	1.61 **	5.57 ***	3.52 ***

Where *: p<0.05, **: p<0.01, ***: p<0.001

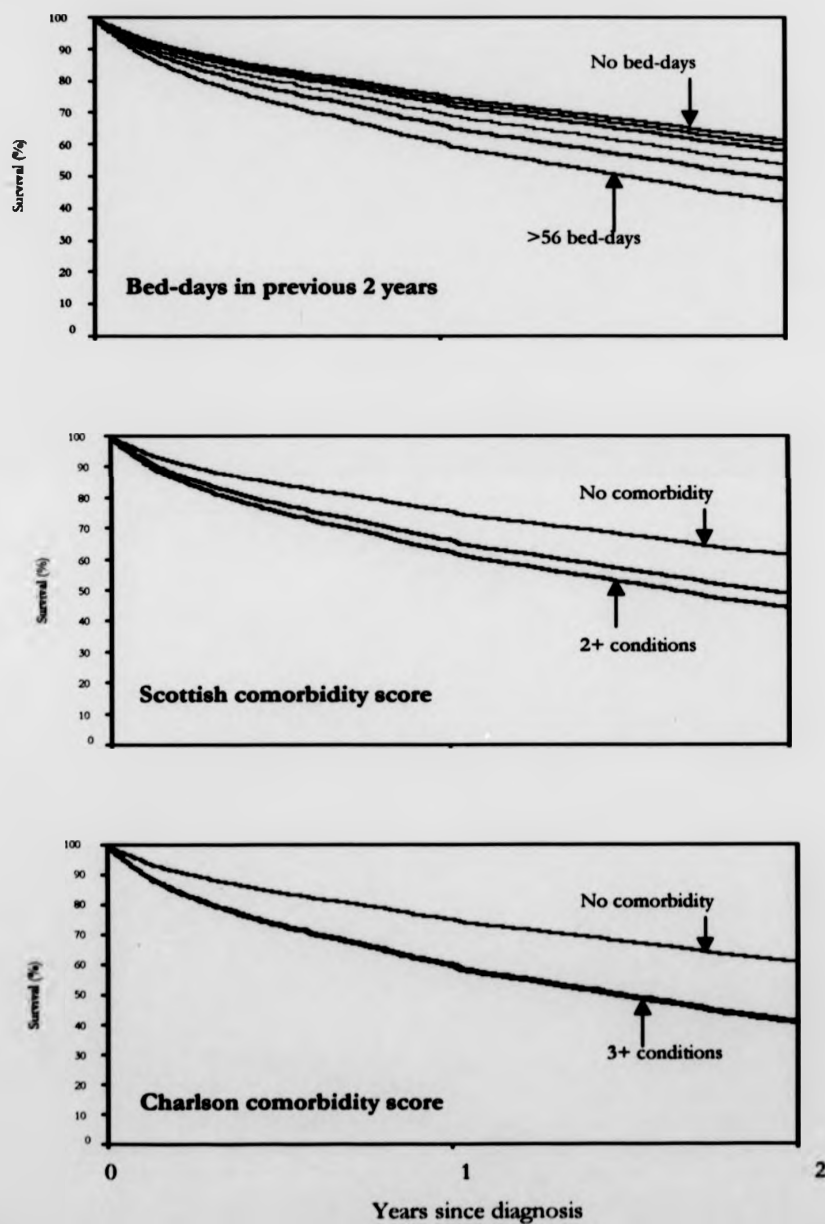
¹ Cancer-related bed-days were defined as inpatient stays with cancer mentioned in one of the diagnosis fields

² Adjusted for tumour stage

It is difficult to decide whether it is only a few specific diseases that are important as comorbid factors in cancer survival, or if it is the overall burden of disease that matters. Certainly from these analyses, it would appear to be a combination. Some diseases, such as myocardial infarction or stroke, might be expected to have a strong impact on prognosis from cancer; however, older patients generally have more comorbid conditions which may be minor, but the accumulation of which may also have a strong impact on survival from cancer. Such minor illnesses might have a simple additive effect on prognosis, or the additional effect might decrease as the number of comorbid conditions increases.

To attempt to overcome problems with uncertainty of how comorbidity affects the survival of cancer patients, I have used both the indices that are based on hospital admissions for specific diseases (Charlson and Scottish indices) and my own index of the overall burden of recent morbidity (all bed-days in the previous two years). The three measures used here are all derived from routine data, and they only reflect co-morbidities resulting in a hospital inpatient admission. There may, of course, be variations in diagnostic criteria and admission threshold for different diseases. Equally, the diseases that require hospital admission and that predict mortality may not be the same as those that predict functional decline or tolerance of cancer treatment, but these issues cannot be addressed using routinely collected data.

Figure 1.3: Patients diagnosed with colorectal cancer in Scotland in 1997: survival (%) by comorbidity score, adjusted for age, sex and tumour stage



Appendix 1.1: Causes of death deemed to be "cancer causes"¹

Cancer diagnosis (ICD-9 codes)	Relevant causes of death (ICD-9 codes)
Oral cancer (141, 143-145)	140-149, 195.0, 196-199, 210.1-210.9, 235.0, 235.1, 238.9, 239.9
Head and neck (140-149, 160, 161)	140-149, 160, 161, 195.0, 196-199, 210, 212.0, 212.1, 235.0, 235.1, 235.6, 238.9, 239.1, 239.9
Oesophagus (150)	150, 151, 159, 195.1, 196-199, 211.0, 211.1, 211.9, 235.2, 235.5, 238.9, 239.0, 239.9
Stomach (151)	150, 151, 159, 195.2, 196-199, 211.0, 211.1, 211.9, 235.2, 235.5, 238.9, 239.0, 239.9
Colon (153), Rectum (154), Large bowel (153+154)	153, 154, 159, 195.2, 195.3, 196-199, 211.3, 211.4, 211.9, 235.2, 235.5, 238.9, 239.0, 239.9
Pancreas (157)	157, 159, 195.2, 196-199, 211.6, 211.7, 211.9, 235.5, 238.9, 239.0, 239.9
Larynx (161)	146, 149, 161, 165, 195.0, 196-199, 210.6, 210.8, 210.9, 212.1, 212.9, 235.6, 235.9, 238.9, 239.1, 239.9
Trachea, bronchus and lung (162)	162, 165, 195.1, 196-199, 212.2, 212.3, 212.9, 235.7, 235.9, 238.9, 239.1, 239.9
Malignant melanoma of the skin (172)	172, 173, 195, 196-199, 216, 238.2, 238.9, 239.2, 239.9
Female breast (174)	174, 195.1, 196-199, 217, 238.3, 238.9, 239.3, 239.9
Cervix uteri (180)	179, 180, 184.9, 195.3, 196-199, 219, 221.9, 236.0, 236.3, 238.9, 239.5, 239.9
Corpus uteri (182)	179, 182, 184.9, 195.2, 195.3, 196-199, 219, 221.9, 236.0, 236.3, 238.9, 239.5, 239.9
Ovary (183)	183, 184.9, 195.2, 195.3, 196-199, 220, 221.9, 236.2, 236.3, 238.9, 239.5, 239.9
Prostate (185)	185, 187.9, 195.3, 196-199, 222.2, 222.9, 236.5, 236.6, 238.9, 239.5, 239.9
Testis (186)	186, 187.5, 187.9, 195.3, 196-199, 222.0, 222.3, 222.9, 236.4, 236.6, 238.9, 239.5, 239.9
Bladder (188)	188, 195.2, 195.3, 196-199, 223.3, 233.9, 236.7, 236.9, 238.9, 239.4, 239.9
Kidney (189)	189, 195.2, 196-199, 223.0, 223.1, 223.9, 236.9, 238.9, 239.5, 239.9
Brain and other CNS (191+192)	191, 192, 196-199, 225, 237.5, 237.6, 237.9, 238.9, 239.6, 239.7, 239.9
Thyroid (193)	193, 195.0, 196-199, 226, 237.4, 238.9, 239.7, 239.9
Non-Hodgkin's lymphoma (200+202), Hodgkin's disease (201), Multiple myeloma (203), Leukaemia (204-208)	200-208, 229.0, 238.5, 238.6, 238.7, 238.9, 239.9

Source: Scottish Cancer Intelligence Unit (2000)¹

¹ ICD-9 codes 196-198 are included although they are not intended to be used for coding the underlying cause of death

Appendix 1.2: World Standard Cancer Patient Population: percentage of patients in each age group

Cancer Group (ICD-9 code)	Age group						
	15-44	45-54	55-64	65-74	75-84	85-99	15-99
Head and Neck (140-149)	18.1	19.2	23.3	19.0	14.7	5.6	100.0
Oesophagus (150)	10.6	16.6	22.7	22.8	19.2	8.2	100.0
Stomach (151)	12.0	15.5	19.4	21.9	21.2	10.0	100.0
Large bowel (153-154)	8.6	10.8	17.0	22.3	26.6	14.6	100.0
Pancreas (157)	10.3	13.7	17.4	21.8	24.0	12.8	100.0
Larynx (161)	11.3	18.4	26.1	21.6	16.1	6.4	100.0
Trachea, bronchus and lung (162)	7.6	13.6	23.0	24.2	21.8	9.8	100.0
Malignant melanoma of the skin (172)	25.4	17.8	18.1	17.1	15.1	6.5	100.0
Breast (174)	22.2	20.5	19.9	17.2	14.2	5.9	100.0
Cervix uteri (180)	28.3	24.1	20.7	14.5	9.3	3.0	100.0
Corpus uteri (182)	11.1	18.9	27.2	21.6	15.2	5.9	100.0
Ovary (183)	23.7	19.5	21.6	17.4	13.0	4.9	100.0
Prostate (185)	0.6	2.4	9.5	20.8	38.2	28.5	100.0
Testis (186)	80.4	10.3	4.7	2.4	1.6	0.5	100.0
Bladder (188)	6.9	10.2	17.9	23.3	27.0	14.6	100.0
Kidney (189)	11.6	14.1	23.3	22.5	19.8	8.7	100.0
Lymphomas and multiple myeloma (200-203)	25.5	14.4	17.6	18.1	16.8	7.6	100.0
All malignant neoplasms (140-208) ¹	32.4	12.5	14.7	16.2	16.4	7.8	100.0

Source: Black and Bashir (1999)²⁸

¹ Excluding non-melanoma skin cancer (ICD-9 173)

Appendix 1.3: Charlson comorbidity index, with optional age addition

Comorbidity	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease (except hemiplegia)	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes (without complications)	1
Diabetes with end organ damage	2
Hemiplegia	2
Moderate or severe renal disease	2
2 nd solid tumour (non-metastatic)	2
Leukaemia	2
Lymphoma, multiple myeloma	2
Moderate or severe liver disease	3
2 nd metastatic tumour	6
AIDS	6

Total points: _____

OPTIONAL EXTENSION

Age	Score
50-59	1
60-69	2
70-79	3
80-89	4
90-99	5

Total combined points (comorbidity+age): _____

Source: Charlson *et al.* (1987)⁷²

MATERIALS AND DEFINITIONS

Scottish cancer registry database (SOCRATES)

The Scottish cancer registry has been collecting population-based information on cancer since 1958. Details available for each case include personal, demographic and diagnosis information (site, histology^a, behaviour, histological confirmation, date and hospital of diagnosis). For patients diagnosed from 1997 onwards further information has been collected including tumour stage (for breast, cervical and colorectal cancer), tumour grade, more hospital details, and treatment information (dates and locations of surgery, chemotherapy, radiotherapy and hormone therapy). In 1997 the tumour-based database was converted into a patient-based database, and was named SOCRATES (Scottish Open Cancer Registration And Tumour Enumeration System).

Potentially new cases are identified from a number of sources, including hospital inpatient discharge records (SMR01s), pathology and oncology databases, and death records. The information is linked using probability matching (described later) and a provisional registration created. Cancer Registration Officers (CROs) visit the hospitals and pull the medical records for these provisional registrations and the registration is then either confirmed, in which case extra information is collected from the medical notes, or deleted if the patient did not in fact have cancer. The hospital visit does not occur until at least six months after the cancer diagnosis to allow treatment details to accumulate.

There are approximately 24 000 new diagnoses of malignant disease entered onto SOCRATES each year. Studies of the data quality suggest that it is high, both in terms of accuracy and completeness of ascertainment⁷⁶⁻⁷⁸.

^a Histology is not available for the whole period from 1958.

Timeliness of registrations

Timeliness is a measure of the time delay between the diagnosis and registration of cancers. Some delay is desirable in order to obtain complete information on initial treatment delivered, so registries are not expected to fully register a patient until at least 6 months after their diagnosis unless they have died within this time interval. The UK Association of Cancer Registries (UKACR) recommend that all cases diagnosed in a given year should be registered 18 months after that year end (for example, all cases diagnosed in 1997 should be registered by mid 1999)⁷⁹. Prior to the introduction of the new computer system (SOCRATES) the Scottish registry was very timely. However, with the change over and training for collection of the extra variables a backlog of registrations has occurred and timeliness in Scotland currently falls behind other registries in Great Britain (Table 2.1). For this reason, it was only possible to consider cases diagnosed up to the end of 1997 in this thesis.

Table 2.1: Timeliness¹ of registering Scottish cancer data² compared to Great Britain

Cancer Registry	% 1996 by mid 1998		% 1997 by mid 1999		% 1998 by mid 2000		% 1999 by mid 2001	
	Initial ³	Full ⁴	Initial ³	Full ⁴	Initial ³	Full ⁴	Initial ³	Full ⁴
Scotland	0	103	44	74	35	44	95	30
Average for Great Britain	30	89	30	80	9	87	26	75

Source: UKACR QA Reports 1998, 1999, 2000 and 2001^{79, 82}

¹ 90% of all cases diagnosed in a given calendar year should be completed and entered onto the registry computer system within 18 months of the end of the calendar year

² All invasive cases excluding non-melanoma skin cancer

³ Initial covers cases where not all the basic information has been received or validity has not been confirmed (in Scotland many of these will turn out to be false registrations)

⁴ Full is defined as 'of a standard useable for analysis and in publications'

Quality and ascertainment

There is no absolute measure for assessing registry ascertainment and quality. The UKACR Quality Assurance group has drawn up a report recommending a number of methods to assess the quality of registry data. The methods proposed are widely accepted and used, but are also recognised as imperfect measures of quality. The quality and ascertainment of the Scottish cancer registry data for 1997 is now investigated using these methods.

Death Certificate Only registrations

The cancer registry receives all death certificates that mention cancer from the Scottish General Registrars Office (GROS). If the patient is not registered already and there are no

other source records on the registry database, then a death certificate initiated (DCI) registration is created. If no further information can be found about this patient, the only information about the cancer is from the death certificate and the registration will be classified as a death certificate only (DCO) registration for analytical purposes. These cases are often excluded from analyses as the cancer coded on the death certificates may be wrong and there is no information about the genuine time of diagnosis.

The percentage of DCO registrations gives an estimate of the quality of registry data and some indication of ascertainment. A more useful statistic to assess ascertainment would be the DCI rate (the proportion of cases escaping the registration process at diagnosis), which is informative because these are cases that would not have been registered unless a death certificate mentioning cancer had been received, i.e. they were not being picked up from hospital sources. A high proportion of DCI registrations would suggest that non-fatal cases are being under-ascertained, as most DCI registrations are rapidly fatal cases⁸³. Unfortunately, it is not possible to calculate the DCI statistic from the Scottish data at present because death certificate information is entered on to the computer as soon as it arrives rather than after all the other routinely arriving source data has been processed.

The DCO rates for Scotland are amongst the lowest of the registries in Great Britain (Table 2.2) indicating that the Scottish data for patients diagnosed during 1997 is of good quality. Knowledge of changing trends in the DCO rates is important in interpreting survival rates. If a high proportion of DCO registrations are not included in the survival analysis this may lead to over-estimation of true survival, since the survival of these excluded patients has been shown to be poorer, on average, than that of all the other cases^{84,85}. DCO percentages vary by cancer for a variety of reasons⁸⁶ with higher rates in cancers diagnosed in very elderly patients and in cancers with a poor prognosis in Scotland¹.

In the early 1970s in Scotland, information was recorded only on patients who were admitted to hospital, and death certificates were not used as a source of case ascertainment⁸⁷. The missed cases were thought to be patients with poor prognosis who were not considered amenable to treatment. More recently such patients would have been admitted to hospital for diagnosis and possibly therapy, and therefore would be included in the data analysed. More complete cancer registration data, particularly for elderly patients with poor prognosis cancers, would be expected to result in decreased survival rates over time. Additionally,

DCO cases were less likely to be recorded as such in Scotland in 1970s, resulting in DCO cases being included as non-DCO zero-survival cases in analyses. This would lead to an increase in survival rates over time. True non-DCO zero-survival cases are those patients who have died on the date of diagnosis, for instance during an investigative operation. The proportion of DCOs in Scotland rises from 1.7% for patients diagnosed during 1971-75 to 3.4% for patients diagnosed during 1991-95¹. The percentage of cases with non-DCO zero-survival have decreased¹, possibly due to earlier presentation and improvements in diagnostic techniques, as well as the problem mentioned above. These changes may have some influence on the survival trends presented in Chapter 3.

Table 2.2: Quality and ascertainment of the Scottish data compared to Great Britain: patients diagnosed in 1997¹

Cancer Registry	% DCO ²	%MV ³	M:I ratio ⁴
Scotland	0.4	84.9	58.8
Average for Great Britain	4.7	80.8	58.4

Source: UKACR QA Report 2000⁷⁹

1 All invasive cases excluding non-melanoma skin cancer

2 DCO (death certificate only) registrations are those where the only source is the death certificate despite exhaustive searching for information.

3 The %MV (microscopically verified) includes cases with histology, cytology or peripheral blood reports.

4 The M:I (Mortality/Incidence) ratio is calculated using official mortality figures from ONS and GROS

Microscopic verification

The percentage of cases diagnosed microscopically (%MV) has been used by the International Agency for Research on Cancer⁸⁰ as an indicator of data quality: a very high %MV may indicate under-ascertainment due too great a reliance on pathology by the registry, whereas a very low %MV may indicate that registry information is of poor quality. The definition relates to the basis of the diagnosis made by the treating clinician (which is outside the registry's control) as well as the availability of the information to the registry, although the registry may not have seen the pathology report. For patients diagnosed during 1997, the Scottish cancer registry has microscopic verification rates which are higher than the average for Great Britain (Table 2.2) indicating good quality of diagnostic information, but not too high as to worry about over reliance on pathology reports for registration.

Trends in proportion of microscopically verified cases in Scotland over time show that the accuracy of diagnoses of cancer reported has improved since the early 1970s¹. Improved understanding of the symptoms of cancer and the increasing availability of biochemical and other diagnostic techniques (for which no information is currently collected in the Scottish cancer registry) may have an important influence on survival rates for particular cancer sites. Modan *et al.*⁸⁹ argue that the apparent increases in brain tumour incidence reported for most Western countries can be attributed to the increasing availability of a non-invasive diagnostic technique (computed axial tomography) and changing attitudes towards the diagnosis of the elderly. Increasing precision of this kind would be expected to decrease survival rates as poor prognosis patients would be correctly classified and the numbers of cases not detected or coded to the 'unspecified primary site' category correspondingly reduced. Improved diagnostic precision is recognised with each change in the international classification of diseases (ICD8, ICD9, ICD10), with a larger variety of codes becoming available. These changes can also influence survival rates and are often not easy to measure.

Mortality to Incidence ratio

The mortality to incidence ratio gives an indication of under- or over-ascertainment. It is calculated as

$$\text{M:I} = \frac{\text{Deaths certified in specified period, with diagnosis C as underlying}}{\text{Incident cases in same period with diagnosis C}}$$

This measure looks at diagnoses and deaths in a specific period, and does not apply to the same patients as the deaths can occur in patients diagnosed over a long period of time. However, when there have been no major changes in incidence or prognosis for a particular tumour site, the M:I ratio is equivalent to one minus the survival probability. The M:I ratio is difficult to interpret if there are significant trends in incidence (for example, due to screening) or survival (for example, new successful treatment), or if the cause of death information is thought to be poor.

If the M:I ratio is greater than 1.0, then under-registration is suspected. However a high ratio may be expected in the ill-defined sites (such as ICD-9 159, 179, 199) and metastatic sites such as liver. The M:I ratio by site should be relatively constant across somewhere like Great Britain where death registration, diagnostic practice, and prognosis are fairly uniform.

The M:I ratio for Scotland is very similar to the average of Great Britain, suggesting that there are no problems in case ascertainment (see Table 2.2).

Table 2.3: Completeness¹ of the Scottish data² compared to Great Britain: patients diagnosed during 1997

Database variable	Scotland	Average for Great Britain
Patient's name	100.0	100.0
Patient's address	100.0	100.0
Post code	100.0	99.7
Sex	100.0	100.0
Date of birth	100.0	100.0
NHS number	21.4	56.0
Anniversary (diagnosis) date	100.0	99.4
Site of primary growth	94.9	94.4
Date of death (where dead)	100.0	99.9
Type of growth	86.9	82.1
Behaviour of growth	100.0	98.5
Basis of diagnosis	99.7	94.5
Treatment codes (% yes)		
Surgery	51.0	48.3
Radiotherapy	27.9	22.7
Chemotherapy	19.5	15.5
Hormone	15.8	10.3
Tumour stage present ³ and known		
Breast cancer	62.6	51.4
Cervix invasive	87.6	65.8
Colorectal cancer	84.3	56.6
Melanoma cancer	0.0	70.5
Grade - Breast cancer only	62.6	65.5

Source: UKACR QA Report 2000³

¹ Percentage of cases with a valid and informative code on the database

² All invasive cases excluding non-melanoma skin cancer

³ Using any valid staging system; not all registries used the same methods

Completeness of data fields

The completeness of the variables collected by the cancer registry is evident, to a certain extent, from the proportion of DCO and MV registrations. However, poor recording in specific areas can be highlighted by comparing completeness of the variables between cancer registries. Completeness of most of the variables is very high for Scotland (Table 2.3). NHS number is not well recorded, but will improve with a mapping exercise to be undertaken in the registry. The information on stage and grade is higher than the average for Great Britain but is actually lower than the other registries which access the case-notes, indicating that further training of cancer registration officers may be necessary in this area.

Random sample review of 1997 registrations

A review of a random sample of 3 175 registrations, for patients diagnosed in 1997, was conducted by the quality assurance and accreditation unit in ISD Scotland. We then compared the re-extracted data (from medical records) to the data on the registry database to assess the accuracy of the cancer registry data⁹⁰ (Table 2.4). Although there was exact agreement on the allocation of incidence date in only 2 384 (75%) cases, the re-abstracted incidence date was within six weeks of the registered date in 3 013 (95%) cases. Discrepancies in grade of differentiation, staging variables and oestrogen receptor (ER) status were largely due to variables being recorded as 'not known' on one database but allocated to a specified category or value on the other. The implications of the results of the QA exercise on the analyses in this thesis are reviewed in the general discussion.

Table 2.4: Review of random sample of patients diagnosed with cancer in Scotland in 1997

Registry database variable	Number of cases compared	Percentage of discrepancies
Incidence date	3,175	24.5
ICD10 (3 digit)	3,175	3.1
Histological verification	3,175	2.0
Morphology code	3,175	18.8
Method of detection	3,175	3.4
Date of birth	3,175	1.3
Sex	3,175	0.0
Postcode	3,175	5.8
Grade	3,175	9.3
Breast clinical size	461	18.2
Breast clinical nodal status	461	17.1
Breast clinical metastatic status	461	10.2
Breast tumour size	461	17.6
Breast nodes examined?	461	11.1
Number of nodes examined	461	3.5
Any positive nodes?	461	1.5
Number of positive nodes	461	2.4
Breast ER status	461	4.8
Colorectal stage	457	13.3
Surgery	3,175	4.0
Date of 1 st surgery	1,769	16.5
Hospital of 1 st surgery	1,769	7.9
Treated with RT	3,175	1.9
Date 1 st RT	954	24.2
Hospital of 1 st RT	954	6.4
Chemotherapy	3,175	1.7
Date 1 st chemotherapy	689	15.4
Hormone therapy	3,175	1.7
Date 1 st hormone therapy	559	17.5

Source: Brewster *et al.*⁹⁰

Definitions

Disease classification and diagnostic details from SOCRATES

The anatomical location (topography) of the tumour, ideally the site of origin of the primary tumour, is recorded to the 10th revision of the International Classification of Disease (ICD-10)⁹¹ for cases diagnosed in 1997 (DCOs are recorded to ICD-9, necessarily, as GROS deaths are coded this way). The main primary site of the tumour is denoted by the first three digits of the ICD code, and a more precise indication of the origin of the tumour (sub-site) is denoted by the fourth digit. The tumour type is the morphological type of the tumour as determined by a pathologist either on the basis of histology or cytology. It is based on the second revision of the International Classification of Diseases for oncology (ICD-O2)⁹². When two (or more) notifications with different morphology codes are received for the same tumour, then the more specific ICD-O2 morphology code is used.

Identification of the histology of the malignancy by microscopical verification of a specimen is generally accepted as the most accurate method of diagnosis. The method of diagnosis is recorded as clinical only, clinical investigation, exploratory surgery/endoscopy/autopsy, biochemical/immunological tests, cytology, histology of metastasis, histology of primary, or autopsy (with histology), in a hierarchical manner. Whether the tumour was microscopically verified is also recorded.

The method of first detection is recorded as screening examination (e.g. routine cervical smear or mammogram in the absence of symptoms), incidental findings during life (e.g. on examination/at surgery for an unrelated reason), clinical presentation with relevant symptoms or signs, or incidental findings at autopsy where cancer was previously unsuspected.

Tumour grade is an indication of how rapidly the tumour is extending, as determined from the pathology report. For most cancers the ICD-O/UICC (Union Internationale Contre le Cancer) system is used:

Grade I – Well differentiated or low grade

Grade II – Moderately (well) differentiated or intermediate grade or average

Grade III – Poorly differentiated or high grade

Grade IV – Undifferentiated or anaplastic

If the description of the tumour overlaps categories then the worst mentioned grade is chosen. The exceptions to this coding system are breast cancer where the Nottingham grading system is used, prostate cancer where the Gleason score is used and for T-Cell and B-Cell lymphomas and leukaemias where the origin takes priority over grade.

Incidence date

The incidence date is defined as the date that the cancer in question becomes formally known to NHS Scotland as follows:

- (a) For patients seen as outpatients and/or day cases and/or inpatients (other than long stay or residential) this is the earliest available date from the following:
 - Date of first consultation as an outpatient relating to the diagnosis
 - Date of first pathology report confirming the diagnosis
 - Date of first admission to hospital relating to the diagnosis
 - Date of first hospital-initiated treatment for the condition
- (b) For long stay or residential patients, or patients receiving care at home:
 - Date of diagnosis (or best estimate)
- (c) For death certificate only cases, and for cases first diagnosed by autopsy:
 - Date of death
- (d) For patients seen and diagnosed by their GP only:
 - Date of diagnosis (or best estimate)

Additionally, the date of first positive mammogram is used for patients detected through breast screening and the date patients commenced on Tamoxifen is used if it was prescribed by their GP before attending hospital.

Disease stage

Tumour stage is a measure of the extent to which the disease has spread at the time of diagnosis. Of the cancers covered in detail in this thesis, colorectal and breast have stage information available on SOCRATES.



Colorectal cancer

Dukes' staging classification. This is primarily based on histological findings and is gained from the pathology report plus a search of the medical notes for evidence of distant metastases. The options are:

- A Tumour limited to muscularis propria, regional lymph nodes negative
- B Tumour invades through muscularis propria into serosa/subserosa or penetrates through the peritoneum but regional lymph nodes negative
- C1 Regional lymph nodes positive but apical node negative
- C2 Regional lymph nodes positive, apical node positive
- C Regional lymph nodes positive (apical node status unknown or not stated)
- D Distant metastases

Regional lymph nodes are the pericolic nodes and perirectal nodes and those located along the ileocolic, right colic, middle colic, left colic, inferior mesenteric and superior rectal (haemorrhoidal) arteries.

Breast cancer

Clinical TNM (Tumour/Node/Metastases) staging classification. If this is not specifically recorded in the medical notes then the CRO will attempt to derive it from the available information. The three measures are recorded as follows:

- cTX Primary tumour cannot be assessed
- cT1 Tumour 2cm or less without direct extension to chest wall or skin
- cT2 Tumour 2cm-5cm without direct extension to chest wall or skin
- cT3 Tumour more than 5cm without direct extension to chest wall or skin
- cT4 Tumour of any size with direct extension to chest wall or skin

- cNX Regional lymph nodes cannot be assessed
- cN0 No regional lymph node metastasis
- cN1 Metastasis to movable ipsilateral axillary node(s)
- cN2 Metastasis to ipsilateral axillary node(s) fixed to one another or to other structures
- cN3 Metastasis to ipsilateral internal mammary lymph node(s)

cMX Presence of distant metastasis cannot be assessed
 cM0 No distant metastasis
 cM1 Distant metastasis

The T, N and M can be analysed separately, or combined into an overall stage score where:

I	T1, N0, M0		
IIA	T1, N1, M0	or	T2, N0, M0
IIB	T2, N1, M0	or	T3, N0, M0
IIIA	T1-2, N2, M0	or	T3, N1-2, M0
IIIB	T4, Any N, M0	or	Any T, N3, M0
IV	Any T, Any N, M1		

Pathological tumour size and information on nodes is also recorded by the CROs. The sizes have been grouped for this project using the same bands as cT1-cT3. Nodal status has been grouped into *positive* if positive nodes were sampled, *negative* if >3 nodes were sampled and all found to be negative, and *negative inadequate* if ≤ 3 nodes were sampled and all found to be negative.

Additionally, for breast cancer, oestrogen receptor (ER) status is recorded as positive or negative where positive is defined as ≥ 20 fmol mg⁻¹ cytosolic protein or ≥ 10% staining.

Morphological type

Grouping of morphologies has been performed for some cancers:

Bladder:	Transitional cell (M81203), Papillary Transitional cell (M81303) and other/unknown
Breast:	Ductal (M85003), Lobular (M85203) and other/unknown
Colon:	No grouping
Rectum:	No grouping
Kidney:	Renal cell (M83123), Clear cell (M83103) and other/unknown
Melanoma:	Superficial (M87434), Lentigo maligna (M87423), Nodular (M87213), Acral (M87443) and other/unknown

Specific site of tumour

For melanoma of the skin, the specific site of the cancer (4th digit of the ICD10 code) was used in the analyses:

Face, head and neck:	C43.0-C43.4
Trunk:	C43.5
Upper limb:	C43.6
Lower limb:	C43.7
Other and unknown:	C43.8-C43.9

Deaths data (GRO database)

Beginning in 1971 each case registered on SOCRATES was followed-up through the National Health Service Central Register (NHSCR), a population-based register of every person resident in Great Britain. The NHSCR records of individuals who were diagnosed with cancer were 'flagged' so that when an individual died the cancer registry could be notified of the date of death. The registry was also notified about any other individuals dying with cancer mentioned on the death certificate.

In 1996, a computerised probability linkage was made between the Scottish general registrars office (GROS) death file for 1974-1994 and the cancer registration file, in order to add up to four causes of death on to all registrations that had a date of death and for which a link could be found. A further annual death link was made of 1995 deaths, and then the whole cancer registration file was internally linked to create a patient-based register, to which 1996 deaths were added, again by an annual link. Thereafter, as part of the new cancer registration process, deaths and causes of death have been added within a few months of the death occurring, although there will also continue to be an annual link at the end of each year to pick up any missed deaths. Deaths are coded to ICD9⁹³ from 1979 to 1999 and ICD10 from 2000 onwards.

Hospital discharge data (SMR01 database)

The Scottish hospital discharge record (SMR01) is an episode-based record relating to all inpatients and day cases discharged from non-psychiatric, non-obstetric wards in Scottish hospitals, and these have been computerised since 1968. A record is formed when a patient is discharged from hospital, changes consultant or is transferred to another hospital or hospital department. Approximately 1 million records are created annually. The range of information collected was expanded and codes changed from April 1996 with the introduction of the core patient profile information system (COPPIH).

SMR01s contain clinical and non-clinical data including information on locations and transfers, waiting times, referral types, diagnostic information and operation and procedure information. The database has not been widely utilised to assess public health issues relating to cancer.

Quality and ascertainment

There is no information on the ascertainment of SMR01s to my knowledge. However, since 1989, information from the SMR01s has been used to plan the financial management of hospitals so this should ensure that ascertainment is high.

Completion of the SMR01 is often delegated to clerical staff and unsupervised by clinicians, making quality assessment very important. Detailed quality assessments of the SMR01 data, using the full medical records, are carried out every few years by the quality assurance and accreditation unit in ISD Scotland. An assessment of discharges in 2000 is currently underway, but the most recent results currently available at a national level are from a 1% assessment of episodes from 1996/97⁴. This study and a previous one conducted on episodes from 1994 both indicate that personal information is over 99% accurate (Table 2.5). However, the postcode field has actually reduced in accuracy over time (from 96.6% in 1994 to 92.3% in 1996/97) which is a concern when conducting linkage work.

The main diagnostic code was 89% accurate, a slight reduction on the 1994 figure that could be due to the change from ICD9 to ICD10 during 1996. The most frequently occurring errors concerned the wrong use of check cystoscopy and check endoscopy, errors relating to symptoms and signs and accuracy of recording angina and myocardial infarction. Cancer

was not highlighted as a problem coding area. Of more concern is the variation in accuracy of main diagnosis between hospitals from 96.6% to 79.8% (data not shown).

Table 2.5: Accuracy of the SMR01 database for patient discharges during 1994 and 1996/7

Database variable	Percentage accuracy	
	1994	1996/97
Hospital patient identifier	99.9	100
Surname	99.8	99.9
Date of birth	99.9	99.9
Postcode	96.6	92.3
Specialty	99.9	99.9
Date placed on waiting list	90.2	89.9
Waiting list type	N/A	96.7
Type of admission	N/A	97.7
Admission/Transfer from	98.6	97.3
Date of admission	99.8	99.7
Date of discharge	99.3	99.5
Main diagnosis (3 digit)	89.9	89.3
Other diagnoses (3 digit)	89.9	90.7
Main operation/procedure (3 digit)	93.9	94.7
Other operations/procedures (3 digit)	90.7	93.2

Source: Quality assessment and accreditation unit (1998)³⁴

Another five diagnoses fields are available for recording other diagnoses that coexist or develop during an episode of care and affect the management of the patient. The variation in accuracy between hospitals ranged from 100% to 77.8%, and completeness of recording ranged from 95.9% to 60% (with an outlier of 38.7%).

The accuracy of coding of main operation/procedure was 95% in 1996/7 and had been increasing since the OPCS4 classification came in to operation in 1989. The main errors were in the wrong use of diagnostic endoscopic examination codes. The QA group found some under-reporting of non-operations including radiotherapy and intravenous chemotherapy. Accuracy of the main operation/procedure ranged from 100% to 85.5% between hospitals, and the completeness ranged from 100% to 89.1%. The accuracy of the other operation/procedure codes had also increased, with accuracy and completeness similar to the main operation/procedure field.

Probability matching

The potential for bringing records together on a patient basis was first outlined by Heasman in 1968. The basis of forming a linked data set is the comparison of two records, and the decision as to whether or not they relate to the same person. However, due to errors in recording, exact matching could miss many true links. To allow for imperfections in the data, the Scottish Record Linkage System uses methods of probability matching⁹⁵ which has been developed over the past 35 years in Canada⁹⁶, Oxford⁹⁷ and in Scotland⁹⁸. A computer matching algorithm calculates a score for each pair of records; the "odds" that they belong to the same person. The overall score is the sum of scores derived from the comparison of each item of identifying information, weighted according to the rarity of the information (e.g. the initial Z in a person's name has a high weight). Similar negative weightings are applied to levels of disagreement between items. The identifying information used is:

Surname (and its phonetic code to overcome differences in spelling)

First initial (also full forename and second initial when available)

Sex

Year, month and day of birth

Postcode

Date of death, if available

The phonetic code used is the Soundex coding system which reduces a name to a code consisting of the leading letter followed by 3 digits. All the vowels after the first letter are ignored, as are W and H. The remaining letters are coded as 1 (B,P,F,V), 3 (D,T), 4 (L), 5 (M,N), 6 (R), and 2 (all other consonants). If the name has fewer than 3 coded letters, trailing zeros are added. A Soundex weight is assigned to each code, reflecting the rarity of the Soundex code throughout the Scottish population, with a maximum weighting of 15.00. The Soundex weight is used by the computer matching algorithm in the calculation of the comparison scores.

The records are blocked on (1) phonetic code of surname and first initial, and (2) date of birth. A full comparison is only carried out for records which agree on either of the blocking criteria. A cross-comparison of first and second forename initials is carried out. The threshold (that is, the score at which the decision to link is made) is determined by clerical checking of a sample of records. Subjects with more than one death record, or with

a hospitalisation occurring after a death record are also clerically checked. From an independent check of the quality of linkages carried out by the Scottish record linkage (SRL) team there was a false positive (incorrect links) rate of 3.7% and a false negative (missed links) rate of 1.9% between two incidence databases (3 077 subjects). In that analysis, the rates were higher for non-postcoded data (4.2% false positive and 2.4% false negative). The independent analysis was based on 'clinical' events and would be lower if transfers and additional treatments were included⁹⁹. Linkage with death information was found to be 99% accurate although the sample was small (166 deaths). A previous investigation found linkage with death information to be 98% accurate⁹⁵.

The SRL team have created a linked database which contains (as at September 2000) information on all SMR01s for patients discharged from hospital between January 1981 and September 1999, cancer registrations for patients diagnosed between January 1980 and December 1997 and deaths from January 1980 to September 1999. The records are stored together in a flat file, in chronological order, retaining their original unlinked format and preceded by the unique personal identifier for each patient group. The database is updated at quarter yearly intervals.

Setting up the working data file

As at September 2000 there were 38 206 cancers on the linked database and 38 337 cancers on the SOCRATES database with a 1997 diagnosis date (figures include non-melanoma skin cancers and non-malignant tumours). The extra 131 cancers on the SOCRATES system were registered after the linkage was performed. A selection of cancers are considered for analysis in the main part of this thesis (see chapter 4 for rationale) including bladder (ICD-9 188, ICD-10 C67), breast (174, C50), colon (153, C18), rectum (154, C20) and kidney (189, C64) cancers and malignant melanoma of the skin (172, C43).

Exclusions

For DCO registrations the date of diagnosis is unknown so these cases are excluded from survival analyses. However, when analysing survival by deprivation group it may actually be appropriate to include DCO cases, because deprivation factors could have contributed to the cancer not being registered¹⁰⁰. In this dataset there were very few DCO registrations and little variation in the number of DCOs by deprivation category (data not shown) so it

was assumed reasonable to exclude the DCOs from the analysis. If time from diagnosis to death was zero days and the case was not a DCO then the date of diagnosis was re-coded to one day earlier to ensure the inclusion of the case in the analysis (the STATA statistical package used for the analyses does not allow cases with zero survival in survival analyses).

The small number of patients (n=30) diagnosed with cancer at young ages were excluded from the analysis, including bladder, kidney and rectal cancers in under 30s, colon and breast cancers in under 25s, and melanoma of the skin in the under 15s. Patients with two independent cancers diagnosed at the same cancer site on the same day are only included in the analysis for that cancer site once. Therefore, 54 breast, 38 colon, 2 kidney, and 7 rectal cancers, and 1 melanoma of the skin were excluded from the analyses.

A working file was set up, containing all the SOCRATES fields of interest, for the 8 739 patients fitting the inclusion criteria who were diagnosed with one of the cancers of interest in 1997. For these patients the linkage number (from the linked database) was added where available (8 719 records; 99.8%). As a result of adding the linkage number, 25 duplicate registrations were identified and the duplicate removed leaving 8 714 cases (Table 2.6). Patients without an SMR01 history (146 patients; 1.7%) were included in the working file with their SMR01 variables set to "unknown". All SMR01 and death records were included in the analyses.

Table 2.6: Cases available for analysis, Scotland, 1997

Cancer	Number on SOCRATES	Number on the linked database	Number with an SMR01 history
Bladder	1,209	1,203	1,195
Breast	3,309	3,307	3,259
Colon	2,148	2,141	2,121
Kidney	487	485	479
Melanoma	673	671	636
Rectum	888	887	878
Total ¹	8,714	8,694	8,568

¹ 52 individuals appear in more than one cancer group so are counted twice in the totals

Creating and defining the variables

The SOCRATES variables

Variables on patient demographics, diagnosis, hospitals and treatment were selected from the SOCRATES database. The patients' sex (variable name in final dataset: *sex*), date of birth (in order to assign *age*), and postcode sector of residence at diagnosis (*postcd*) were included in the dataset.

Diagnostic information included the incidence date (*diagdt*), diagnosis (*diag*), morphology code (*morph*), histological verification (*histver*, coded as yes, no or unknown), method of first detection (*methdet*, recoded as screening or other), grade (*grade*), and for breast cancer, the oestrogen receptor status (*erstatus*). Information on stage of the tumour at diagnosis was available for colorectal cancers (*crstage*) and breast cancer (*cT*, *cN*, *cM*, *pT* and *pN*). For breast cancer, for field *cN* of the cTNM, it was necessary to combine the *cN*=2 and *cN*=3 categories due to the small number of cases (10) with *cN*=3.

The hospital of diagnosis (*hospdiag*) was recorded, along with the hospitals where main surgery, radiotherapy, chemotherapy and hormonal therapy took place (*hospsurg*, *hosprad*, *hospchemo* and *hosphorm*). Treatment information included whether treatment was received (*surgery*, *rt*, *chemo* and *horm*, coded as yes, no, planned or unknown) and whether this was within 6 months of diagnosis, location of radiotherapy (*radprim*, *radmets*, *radoth*), and date the treatment was first received (*dsurg*, *dtrad*, *dtchemo* and *dtorm*). A field was also available indicating whether the patient had been referred to a radiotherapy department (*refrad*). For analysis of the treatment information, the category indicating that treatment was planned at a later date was included with the unknowns due to small numbers. Days between diagnosis and treatment (*days_surg*, *days_rad*, *days_chemo* and *days_horm*) were calculated.

The date of death (*ddth*) and cause1a, 1b, 1c and 2 from the death certificate (*cause1a*, *cause1b*, *cause1c* and *cause2*) were also available. Vital status and days between diagnosis and death (*status2yrs* and *days2yrs*) were calculated and patients still alive were censored at two years after diagnosis as complete death data was only available up to the end of 1999.

Multiple primary cancers

Patients with previous or concurrent primaries were kept in the working file. A field *multprim* was created to identify them, with the following codes:

- Y First primary
- Y2 First primary with another independent primary diagnosed at same time
- N1 Not first primary - previous primary at a different site
- N2 Not first primary - previous primary at the same site

Non-malignant cancers and non-melanoma skin cancers were not considered as previous cancers when allocating the flag. For patients with previous or concurrent primary tumours, the diagnosis and date of diagnosis fields of the other tumours were added to the patient record (*diag1, dtdiag1, diag2, dtdiag2, diag3, diag4* and *dtdiag3,4*).

Table 2.7: Multiple primary information for selected cancers, Scotland, 1997

Cancer	Y ¹	Y2 ²	N1 ³	N2 ⁴
Bladder	1,092	2	110	5
Breast	3,104	0	105	100
Colon	1,939	18	148	43
Kidney	445	4	36	2
Melanoma	626	2	44	1
Rectum	813	14	59	2
Total ⁵	8,019	40	502	153

¹ First primary malignancy

² First primary with another primary diagnosed on the same day at another cancer site

³ Not first primary, previous primary at another cancer site

⁴ Not first primary, previous primary at the same cancer site

⁵ 52 individuals appear in more than one cancer group so are counted twice in the totals

Overall, 40 patients had two primaries at different cancer sites diagnosed on the same day, 502 had a previous primary at a different cancer site and 153 had a previous primary at the same cancer site (Table 2.7). All patients with a previous primary or a simultaneous primary at another cancer site were included in the analyses, because this could be an important factor related to deprivation-specific differences in survival.

Age groups

An age group (*agegrp*) variable was created specific to each cancer. The selection was made by visual inspection of Kaplan-Meier survival curves of each 5-year age band calculated as age at diagnosis. Concurrent age groups with similar survival curves in the first two years after diagnosis were then grouped together. A minimum of 50 cases per age group was allowed. The age groupings and proportion of cases within each age group were as follows:

Bladder:	30-49 (3%), 50-59 (12%), 60-69 (28%), 70-79 (35%) and 80+ (22%)
Breast:	25-34 (2%), 35-49 (19%), 50-59 (26%), 60-69 (21%), 70-74 (10%), 75-79 (9%), 80-84 (6%) and 85+ (7%)
Colon:	25-49 (5%), 50-59 (11%), 60-69 (24%), 70-74 (17%), 75-79 (19%), 80-84 (15%) and 85+ (11%)
Rectum:	30-44 (3%), 45-49 (3%), 50-59 (14%), 60-69 (25%), 70-79 (33%), 80-84 (13%) and 85+ (9%)
Kidney:	0-49 (10%), 50-64 (32%), 65-74 (38%), 75-79 (11%) and 80+ (10%)
Melanoma:	15-49 (40%), 50-59 (16%), 60-64 (8%), 65-69 (7%), 70-74 (8%), 75-79 (10%) and 80+ (11%)

Postcode information

Standard look-up tables were applied to the postcode information to assign each patient to a health board of residence at diagnosis (*hb*), a Carstairs deprivation quintile (*depcat*) based on the 1991 census (see Chapter 1) and to identify the place of residence as urban or rural (*urb_rur*).

There are currently 15 Health Boards in Scotland, and for the purposes of analysis the smaller Health Boards were merged with neighbouring Health Boards to give 10 areas for analysis. Orkney, Shetland and the Western Isles were combined with the Highlands, Borders with Lothian, and Dumfries and Galloway with Ayrshire and Arran.

The basic urban or rural variable defined by the GROS was used. The total population for a given area is found by taking each town and adding each directly adjacent town i.e. those which make up one continuous area. All postcodes that lie within each continuous area are

then assigned a category based on the population for the total continuous area. The categories are:

- 1 Over 1,000,000 people
- 2 100,000 - 999,999
- 3 10,000 - 99,999
- 4 1,000 - 9,999
- 5 500 - 999
- 6 Not in a locality

These were then grouped with categories 1-2 signifying urban areas and 3-6 signifying rural areas.

Hospitals

The Chief Medical Officers of England and Wales published the Calman-Hine report¹⁰¹ in 1995, recommending that a number of cancers be managed by specialist cancer teams in locations with the necessary specialist resources. The Scottish Cancer Coordinating and Advisory Group (SCCAC) proposed a similar network for Scotland in 1996¹⁰², with the aim that all patients have access to high levels of specialist cancer care to provide optimal treatment. Five regional centres with radiotherapy provision were identified: Raigmore Hospital (Inverness), Aberdeen Royal Infirmary, Ninewells Hospital (Dundee), Western General Hospital (Edinburgh) and the Western Infirmary/Beatson Oncology Centre (Glasgow).

A variable *hosp_surg* based on the numbers of patients receiving their main treatment at each hospital was calculated. The regional centres were included as a separate category. If surgery was performed then the hospital of surgery was identified from SOCRATES or the SMR01, otherwise the main treatment hospital was assigned as the hospital where the first non-surgical treatment was performed (radiotherapy, chemotherapy or hormone therapy).

The *hospsurg* variable was defined:

- 0 Regional centre with radiotherapy provision
- 1 Other hospitals treating large number of patients
- 2 Hospital treating medium to high number of patients
- 3 Hospital treating medium to low number of patients
- 4 Hospital treating low number of patients
- 7 Non-hospital (Hospice, GP, health centre, nursing home, breast screening centre, home only)
- 8 No treatment received

Also, a variable *hospever*, indicating whether the patient was seen at a high workload hospital at any time during their spell was calculated. The *hospever* variable was defined in the same way as the *hospsurg* variable but was assigned on a hierarchical basis (i.e. 1: if the patient had attended a regional centre with radiotherapy provision at any time during the cancer spell; if not then 2: if the patient has attended another high workload hospital during their cancer spell; if not then 3: etc)

The distribution of the numbers of cancer patients receiving treatment at each hospital during the period 1996-1998 were used to define the cut-points of high, medium and low workload hospitals (using the 25th, 50th and 75th percentiles, after restricting this analysis to hospitals treating at least 5 patients per annum). The year-on-year numbers were scrutinised to ensure that hospitals with changing workloads for cancer treatment were not wrongly assigned for the year of interest (1997). The cut points were as follows

Bladder:	High ≥ 49 , Medium to High 34-48, Medium to Low 24-33, Low <24
Breast:	High ≥ 104 , Medium to High 56-103, Medium to Low 15-55, Low <15
Colon:	High ≥ 80 , Medium to High 63-80, Medium to Low 36-62, Low <36
Kidney:	High ≥ 18 , Medium to High 14-17, Medium to Low 12-13, Low <12
Melanoma:	High ≥ 23 , Medium to High 15-22, Medium to Low 12-14, Low <12
Rectum:	High ≥ 50 , Medium to High 36-49, Medium to Low 24-35, Low <24

Waiting times

The time from diagnosis to surgery was calculated and split into two categories: less than two weeks or more than two weeks. Information on other waiting times (e.g. between surgery and radiotherapy) were investigated but not used in the final analyses.

The SMR01 variables

Analysis of SMR01 data is complex because patients may have many SMR01 records and it is often not obvious which is the first visit relating to the cancer diagnosis. A number of variables were constructed to identify important SMR01s. For this purpose, a file was constructed containing all the SMR01 information for the 8 568 cancer cases with an SMR01 history. This file contained 85 530 SMR01s for 8 516 patients, giving an average of 10 SMR01s per person. Overall, 9% of patients had more than 20 SMR01s and 7 patients had over 100 SMR01s.

Identifying records with cancer mentioned

A field was created called *diagadmit* to identify SMR01s that encompassed the cancer diagnosis date and whether these mention the specific cancer (defined as having the same ICD-10 code at the three-digit level) or another cancer:

Y1	Within stay and specific cancer mentioned
Y2	Within stay and another cancer mentioned
Y3	Within stay and cancer not mentioned
N1	Outwith stay and specific cancer mentioned
N2	Outwith stay and another cancer mentioned
N3	Outwith stay and cancer not mentioned

Of the 8 568 patients with an SMR01 history, 8 044 (94%) had an SMR01 mentioning cancer at some point. Overall, 2 345 (27%) patients had their specific cancer mentioned on an SMR01 encompassing the cancer diagnosis and 3 429 (40%) patients had their specific cancer mentioned on an SMR01 with date of admittance during the month after diagnosis. Of those not falling into one of these two categories, 294 (3%) had a different cancer mentioned on an SMR01 either encompassing or in the month after diagnosis; 74 (1%) had the specific cancer mentioned before diagnosis; 53 (1%) had a different cancer mentioned

before diagnosis; 1 768 (21%) had the specific cancer more than one month after diagnosis; and 81 (1%) had a different cancer mentioned more than one month after diagnosis (Table 2.8).

Table 2.8: Number and percentage of patients with an SMR01 containing a cancer diagnosis

Cancer	A=Y1+Y2 ¹		B=N1+N2 ² (excluding those in A)		C=Y3+N3 ³ (excluding those in A or B)	
Bladder	489	40.9	660	55.2	46	3.8
Breast	431	13.2	2,649	81.3	179	5.5
Colon	1,083	51.1	951	44.8	87	4.1
Kidney	195	40.7	255	53.2	29	6.1
Melanoma	72	11.3	415	64.3	149	23.4
Rectum	301	34.3	543	61.8	34	3.9
Total⁴	2,571	30.1	5,473	63.9	524	6.1

¹ Cancer mentioned on SMR01 encompassing the cancer diagnosis date

² Cancer mentioned on an SMR01 not encompassing the cancer diagnosis date

³ Cancer not mentioned on any SMR01s

⁴ 52 individuals appear in more than one cancer group so are counted twice in the totals

Identifying the first and subsequent records relating to the cancer diagnosis

When SRL perform the linkage of the dataset, they add in a variable that identifies all records relating to a 'continuous inpatient stay' (cis), linking transfers during a hospital visit which are all recorded as separate SMR01s. Apart from using information on whether the type of discharge of the first record or the type of admission of the second record was a transfer, the decision on what constitutes a CIS also hinges on the length of the interval between the discharge of one record and the admittance of the next. The records are linked as a CIS if this interval is negative, or if the interval is less than 2 days and type of discharge or admission recorded as transfer. The "type of admission" (*tadm*), "admission/transfer from" (*adtf*), "date of admission" (*dtadmit*) and "date of discharge" (*dtdis*) fields are used. Incremental numbers are used in the CIS field to link the records.

For this thesis, further identification of related records was needed so that the initial SMR01 (i.e. the one representing the initial hospitalisation resulting in the diagnosis of the cancer) and all subsequent SMR01s relating to the cancer could be identified. This group of records has been called the cancer spell, and spells are identified using the *tadm*, *adtf*, *dtadmit*, *dtdis*, CIS, specialty (*spec*) and diagnoses (*diag1-6*) fields. The specialty field was used to identify return visits for radiotherapy and the diagnosis fields were used to identify admissions for

common cancer symptoms. Once all records in a spell have been identified, incremental numbers are assigned (*order*) to link the records and the type of record in the spell is recorded (*spell*):

- 99 Record starts a new spell
- 88 Record starts a new spell but manual check needed
- 1 Continuous inpatient stay within a spell
- 2 Subsequent related visit within a spell

It was important to correctly identify the SMR01 marking the start of the hospitalisation due to the cancer of interest (the index SMR01) so that relevant information from this record onwards could be extracted for the working file. If the patient visited with symptoms prior to diagnosis then this record would be identified as the index SMR01, otherwise an algorithm was used to identify the index record and the rest of the cancer spell (see Appendix 2.1). A visual check of the accuracy of the algorithm was performed using the kidney data (479 patients) by assigning the index SMR01 from visual inspection without knowing how the algorithm had assigned it. Overall, 26 (5%) records were incorrectly assigned by the algorithm. The decision rules for these cases were too diverse to be successfully programmed.

Symptom lists were created by examining all the diagnoses reported on the SMR01s in the period 1 year prior to 3 months after the cancer diagnosis. Relevant diagnoses (symptoms) were selected with help from a medical expert and common symptoms requiring urgent referral, as recorded in published referral guidelines for suspected cancer^{9a} were also included (see Appendix 2.2).

The SMR01-related variables described below were computed in two ways:

- (1) All SMR01 records from the index SMR01 to the end of the identified cancer spell were included. When it was not possible to identify an index SMR01 (i.e. if there were no relevant SMR01 records; affecting around 4% of patients) then the date of diagnosis from SOCRATES was used as the index date.

- (2) All SMR01 records from a fixed time interval of 1 month prior to 6 months after diagnosis were included. The six-month time interval was selected to correspond with the time band for collecting treatment information defined by the cancer registry.

Only the variables computed by the second method were used in the final analyses due to difficulties in identifying the cancer spell.

Specialist department

Whether the patient was seen in a specialist department was calculated. The SMR01s in the cancer spell were used to define the variable *specdept* using the specialty code on each SMR01 in the spell. The variable was defined as follows:

- 0 Never seen in a specialist department
- 1 Transferred to a specialist department within 3 months of diagnosis
- 2 Transferred to a specialist department within 3-6 months of diagnosis
- 3 Transferred to a specialist department more than 6 months after diagnosis

The specialist departments were defined as follows:

- Clinical oncology for all cancers
- Medical oncology for all cancers
- Urology for kidney and bladder cancers
- General surgery for breast, colon, rectal and melanoma skin cancers
- Plastic surgery for breast and melanoma skin cancers

Consultant workload

Whether a high-workload consultant saw the patient at some point during their cancer spell (*consworkld*) and, for surgically treated patients, was managing the patient when they had surgery (*surgworkld*) was calculated. The number of patients seen by each consultant was extracted from the SMR01 data and the consultants were then banded into workload groups. The cut-offs for the groups were decided based both the distribution of workloads and bandings previously used in the literature:

Breast:	1-9, 10-29, 30-99, 100+ cases per year
Colorectal:	1-9, 10-19, 20-29, 30+ cases per year
Kidney:	1-4, 5-9, 10+ cases per year
Bladder:	1-9, 10-19, 20-29, 30+ cases per year
Melanoma:	1-9, 10-19, 20-25, 26+ cases per year

Another important factor is whether the surgeon worked in a multidisciplinary team. This information is not collected routinely and so it was not possible to include in this thesis.

Emergency or planned admission

The variable *emerg1* was extracted from the type of admission of the index SMR01 in the cancer spell and defined as follows:

0	Non-emergency
1	Emergency

Operations

Information on whether patients received key operations^b within the cancer spell was extracted from the SMR01 database for breast cancer, and was supplemented by the SOCRATES information on whether treatments were received. The variable *ops* was created and was assigned hierarchically in the order listed:

- 1 Mastectomy (OPCS4 B27)
- 2 Breast conservation surgery (OPCS4 B28, B33-B35)
- 3 Other (B37, L91, S06) and unspecified surgery (surgery=yes on SOCRATES database but SMR01 not coded as above)
- 0 No Surgery with curative intent performed

Type of operation was not taken into account for colon, rectal, kidney or bladder tumours, and was not relevant for melanoma of the skin.

^b Operations included were defined using published information. The Edinburgh clinical coding office validated the codes.

Transfer patterns

The number of transfers between (not within) hospitals during the cancer spell was calculated and a variable *nhosps* was computed:

- 1 No transfers – one hospital throughout
- 2 One – two transfers during spell
- 3 More than two transfers during spell

The number of hospital admissions from home during the period from the date of the index admission up to the date of surgery was also calculated to attempt to investigate differences in the path of cancer care. This variable *nvisits* was defined:

- 1 One continuous inpatient stay
- 2 Two or three visits
- 3 More than three visits

Co-morbidity

Co-morbidity was assessed using three different measures – two based on the burden of specific diseases (Charlson and Scottish indices) and the other based on the time spent in hospital (bed-days index) to give an idea of overall burden of illness (see Chapter 1).

- | | | |
|-----------|---|-----------------------------------|
| Charlson: | 0 | No comorbidity |
| | 1 | Score of 1-2 |
| | 2 | Score of 3+ |
| Scottish: | 0 | No comorbidity |
| | 1 | 1 previous condition |
| | 2 | 2+ previous conditions |
| Bed-days: | 0 | No bed-days in previous 2 years |
| | 1 | 1-4 bed-days in previous 2 years |
| | 2 | 5-10 bed-days in previous 2 years |
| | 3 | 11+ bed-days in previous 2 years |

Appendix 2.1: Algorithm to identify the index cancer SMR01 and subsequent SMR01s in a spell

1. Identify as the beginning of a new spell (spell=99) if one of the diagnosis fields contains a symptom from the list, and the date of admittance is not more than six months prior to diagnosis.
2. Identify as the beginning of a new spell (spell=99) all SMR01s with admittance/transfer from a private or institutional residence whose date of admittance is greater than 7 days since the previous date of discharge, except if they
 - i. Have type of admission recorded as planned transfer
 - ii. Have their specialty recorded as haematology, oncology or urology (as these are usually repeat visits relating to the spell) with admittance less than 6 months since last discharge
 - iii. Have a waiting list type of planned repeat admission (as these are also usually repeat visits relating to the spell) with admittance less than 6 months since last discharge
 - iv. Have the same diagnosis (diag1) as the previous record with admittance less than 2 months since the discharge of the previous record (probably related to the spell)
3. Allocate subsequent SMR01s to the same spell if
 - i. The date of admittance is less than the date of discharge (plus 7 days) of any other records assigned to the spell (spell=1)
 - ii. The specialty is haematology, oncology or urology and the previous discharge date was less than 6 months earlier (spell=2)
 - iii. The diagnosis is the same as the previous record and the discharge date of previous record was less than 2 months previously (spell=2)
 - iv. If the waiting list type is planned repeat admission and the previous discharge date was less than 6 months earlier (spell=2)
4. For those not allocated to a spell, identify the beginning of a new spell for those transferred from accident and emergency (spell=99). Repeat step (3).
5. For those still not allocated to a spell, identify the first SMR01 in each sequential run of unallocated SMR01s as a new spell (spell=88). Repeat step (3).
6. Allocate sequential numbers in the order field, incrementing at each new spell to group together SMR01s occurring within one spell.

Appendix 2.2

Referral guidelines for suspected cancer – common symptoms requiring urgent referral

Cancer	Symptoms	ICD9 code	ICD10 code
Colorectal	Rectal bleeding without anal symptoms	5693	K625
	Palpable right-sided abdominal or rectal (not pelvic) mass	789	R190
	Change of bowel habit to looser or increased frequency of defecation, persistent for 6 weeks	558, 5640	K52, K590
	Iron deficiency anaemia without an obvious cause	280, 2810	D50
Breast	Lump	6117	N63X
	Ulceration	6110	N61X
	Skin nodule or distortion	-	-
	Nipple eczema	6112	N640
	Recent nipple retraction or distortion	6117	N645
Bladder	Macroscopic or microscopic haematuria	5997	N02, R31
Kidney	Macroscopic or microscopic haematuria	5997	N02, R31
	Loin pain	7880	N23
	Renal mass	5939	N28
	Anaemia	280, 2810	D50
	Weight Loss	7832	R634
	Pyrexia	7806	
Melanoma	Pigmented lesions with one or more of the following features Growing in size Mixed or changing colour Changing shape Ulceration Irregular outline Inflammation	7090	R234, R238, R22

Source: Referral guidelines for suspected cancer¹⁰³

CANCER SURVIVAL IN SCOTLAND 1971-1998

Background

One in three people develop cancer during their lifetime, and most people are therefore affected either directly or indirectly with it. Around 25 000 new cancers are diagnosed every year in Scotland, of which half are in people aged under 70 years. Cancer is responsible for a quarter of all deaths in Scotland, with survival among the worst in Europe^{5,6}. Cancer mortality can be reduced both by primary prevention (fewer new cases diagnosed) and by earlier diagnosis leading to more effective and timely treatment (improved survival).

Cancer patient survival is a key indicator of the efficacy and equity of cancer patient management, a process including timely diagnosis, effective treatment, and appropriate care. This chapter provides general analyses of cancer survival in Scotland by period of diagnosis, age, sex and deprivation, giving a background to the more detailed investigation of survival from selected cancers presented in subsequent chapters.

Data and Methods

Data

Trends in cancer survival are presented for patients diagnosed between 1971 and 1995 and followed up until the end of 1998. The start date of 1971 was chosen because prior to that date follow-up of cases was thought to be less complete. The end date was chosen because 1998 was the latest year of complete follow-up at the time of analysis (autumn 1999), and so all patients diagnosed in the period 1991-95 were followed up for at least three years, and the majority for at least five years. The analyses were stratified by the five-year periods 1971-75, 1976-80, 1981-85, 1986-90 and 1991-95. Results are presented for 25 major cancers, together with all malignancies combined (ICD-9 140-208, excluding non-melanoma skin cancer ICD-9 173). Non-melanoma skin cancers were excluded because registration is

known to be incomplete, particularly in earlier years. They are common tumours, and are very rarely fatal. Only adults (aged 15+ years) were considered.

Registrations for patients who live outside Scotland, or have no recorded health board of residence, were excluded. A relatively high proportion (5%) of registrations did not have a health board of residence assigned in the first five-year period analysed, due to the fact that the postcode system was not as commonly used in the early 1970s (only half the registrations had a postcode in this period; Table 3.1). An exploratory analysis of the data for the period 1971-75 was performed, both excluding and including the cases with no residence details. Excluding the patients with no health board of residence led to slightly higher estimates of survival for cancers of the bladder, cervix, ovary and prostate, because for these cancers survival was worse for patients with no health board of residence recorded. This leads to conservative estimates of the gradient of improvement over time. There was no difference in the survival for all other cancers (data not shown).

Only first malignant tumours were included, as patients with a previous malignant tumour are likely to have poorer than average survival. The numbers of second or subsequent malignant tumours increased over the time period due to improvements in registration practice and a longer calendar period over which to accumulate registrations. Diagnoses of non-melanoma skin cancer, which were excluded from the extracted data set, were ignored when identifying multiple malignant tumours. An exploratory analysis of the data for the period 1991-95 was performed, both excluding and including second and subsequent malignant tumours. The estimates were very similar for most cancers, but not for malignant melanoma of the skin and corpus uteri cancers, where a significantly poorer survival was seen when patients who had a previous malignant tumour were included in the analyses (data not shown).

Cancers registered from a death certificate only (DCO) were also excluded, as the true date of diagnosis is unknown for these individuals. It has been shown that the true survival for these patients is lower than average^{84,104}. In Scotland, DCO registrations are more common in the elderly (with 1%, 26%, 31% and 42% of DCO registrations occurring in patients aged <50, 50-69, 70-79 and 80+ years, respectively). They comprise largely lung cancer (32% of DCO registrations; 6% of lung cancer registrations), 'other malignancies' (19%; 6%), large bowel (10%; 3%) and breast cancer (9%; 2%)¹.

Table 3.1: Patients diagnosed with cancer in Scotland during 1971-95: registrations included and excluded from the survival analyses

	Period of diagnosis											
	1971-75		1976-80		1981-85		1986-90		1991-95		Total	
Total registrations ¹	82,132	100%	97,236	100%	106,638	100%	113,186	100%	123,225	100%	522,421	100%
Age < 15 at diagnosis	653	1%	713	1%	584	1%	613	1%	639	1%	3,202	1%
Age > 99 at diagnosis	1	0%	10	0%	29	0%	24	0%	37	0%	101	0%
Total eligible	81,478	99%	96,513	99%	106,025	99%	112,549	99%	122,549	99%	519,118	99%
Excluded from survival analysis (% of eligible)												
Unknown residence or outwith Scotland	4,011	4.9%	41	0.0%	9	0.0%	4	0.0%	7	0.0%	4,072	0.8%
Age unknown	5	0.0%	1	0.0%	0	0.0%	0	0.0%	0	0.0%	6	0.0%
Not first primary malignancy ²	2,056	2.5%	3,761	3.9%	5,354	5.0%	6,958	6.2%	9,331	7.6%	27,460	5.3%
Vital status unknown / migrated	13	0.0%	18	0.0%	46	0.0%	321	0.3%	285	0.2%	683	0.1%
Invalid dates	13	0.0%	1	0.0%	6	0.0%	7	0.0%	29	0.0%	56	0.0%
Death Certificate Only case ³	1,266	1.6%	4,731	4.9%	4,078	3.8%	3,739	3.3%	3,845	3.1%	17,659	3.4%
Total excluded from the survival analysis (% of eligible)	7,364	9%	8,553	9%	9,493	9%	11,029	10%	13,497	11%	49,936	10%
Total included in survival analysis (% of eligible)	74,114	91%	87,960	91%	96,532	91%	101,520	90%	109,052	89%	469,182	90%
Of those included in survival analysis												
Non-DCO zero survival time ⁴	2,849	4%	2,727	3%	2,348	2%	1,835	2%	2,281	2%	12,040	3%
Dead by 31/12/98 but no cause of death on cancer file	27,246	37%	2,039	2%	953	1%	637	1%	403	0%	31,278	7%

Source: Scottish cancer intelligence unit¹

¹ All malignant neoplasms (ICD-9 140-208) excluding non-melanoma skin cancer (ICD-9 173).

² Where a patient's first malignancy was a non-melanoma skin cancer (ICD-9 173) or a non-malignant tumour (ICD-9 210-239) the second malignancy was included in the survival analysis.

³ Registered on the basis of a death certificate diagnosis only (DCO).

⁴ These are not DCO cases but have apparently zero survival.

In total for the whole period, just under half a million records were analysed, and the proportion of cases included in the analyses was fairly consistent over time (ranging from 90.2% for cases diagnosed in 1971-75 to 88.5% for cases diagnosed in 1991-95). The main reasons for exclusion being not a first primary tumour (5.3%), death certificate only registrations (3.4%) and missing postcode (0.8%). Patients with zero survival times, but not DCO, were included in the analysis.

Methods

The methodology is described in detail in Chapter 1.

Observed, cause-specific and relative survival estimates, with 95% confidence intervals, are presented in this chapter. The estimates were computed using the STATA algorithm *strel2*⁴ based on the relative survival approach outlined by Estève *et al* (1990)⁵⁴.

Scottish life tables for single year of age at death from 0-99 years and six periods of death (1971-75, 1976-80, 1981-85, 1986-90, 1991-95, 1996-98) were used in the relative survival analyses. Scottish deprivation-specific life tables were used in the deprivation-specific relative survival analyses, based on deaths occurring around the 1991 census (1990-92) and using populations derived from the 1991 census with adjustment for the known census population undercount.

For each cancer, Appendix 1.1 shows the causes of death which were deemed to be cause-specific. Cause-specific analyses are presented for the period 1991-95, when causes of death on the cancer registration file were most complete (99.6%). For the small numbers of registrations for which the cause of death was not available, it was assumed to be the same as the cancer diagnosis.

The survival estimates were age-standardised, using the world standard cancer patient population⁵⁸ (see Appendix 1.2), to allow valid comparisons between survival rates of a given cancer over time and between deprivation groups. For the time trend analyses, the age bands 15-44, 45-54, 55-64, 65-74, 75-84 and 85-99 years were used. For the deprivation analyses, the age bands 15-54, 55-74 and 75-99 years were used.

If there are fewer than 9 cases in an analysis group, then a survival estimate was not be computed. The following approach was adopted for the calculation of age-standardised survival rates:

- (1) If there were age-specific survival rates available in an earlier (first choice) or later time period then this value was used. The assumption being that differences in survival between time periods will generally be less than differences in survival between age groups and sexes.
- (2) If there were no age-specific survival rates available for any of the time periods then, if possible, a truncated rate was calculated.
- (3) Otherwise no standardised rate was calculated.

As the world standard cancer patient population generally gives a low weight to the younger age groups which have small numbers of cases in Scotland, using approach (1) above will generally only have a very small effect on the overall standardised survival estimate.

The STATA algorithm requires that all patients have greater than zero survival time, so to avoid the exclusion of non-DCO patients with zero survival times, the survival time for these patients was reset to 1 day. If there are no deaths in an analysis group, then the STATA algorithm does not run, and so the estimates were set at 99.99%.

The Carstairs deprivation index⁶⁹ was used as the measure of material deprivation, derived from 1991 census data. Each patient diagnosed between 1991 and 1995 was assigned to a quintile of deprivation, ranging from affluent to deprived.

Results and commentary

The numbers of registrations of malignant neoplasms (excluding non-melanoma skin cancer) in Scotland increased from over 82 000 during 1971-75 to over 123 000 during 1991-95 (Table 3.1). This is due partly to ageing of the population (since cancer is primarily a disease of the elderly)^c but mainly due to a genuine increase in risk of many cancers¹⁰⁵. In addition, ascertainment has probably been more complete since the mid-1970s¹⁰⁶.

^c When cancer-, age- and sex-specific first primary incidence rates for the 1971-75 patients are applied to the 1991-95 population estimates, then we would expect 81 396 cases compared to 109 052 observed cases. Therefore, 20% of the increase between 1971-75 and 1991-95 is a direct consequence population ageing.

Cancers of the testis and cervix are the most common in young adulthood. In older age groups, lung cancer and large bowel cancer, together with prostate cancer and breast cancer are the most frequent forms of the disease, accounting for over 50% of cancers. Over the period studied there were substantial increases in incidence. In particular, oral, oesophageal, prostate and thyroid cancers and malignant melanoma of the skin all showed increases in the number of cases of over 40%. Large increases were also seen for large bowel and breast cancers. Lung cancer increased significantly in females, but reduced in males, and stomach cancer was also declining (Table 3.2).

Table 3.2: Patients diagnosed with cancer in Scotland during 1971-95: number of patients entered into the survival analyses by cancer and time period

Cancer (ICD-9 code)	Period of diagnosis				
	1971-75	1976-80	1981-85	1986-90	1991-95
Oral cancer (141, 143-145)	586	726	917	1,075	1,261
Head and neck (140-149, 160, 161)	2,630	2,985	3,322	3,482	3,874
Oesophagus (150)	1,851	2,269	2,541	2,694	3,293
Stomach (151)	5,845	5,678	5,837	5,328	4,722
Large bowel (153+154)	10,788	11,788	12,788	13,788	14,788
Colon (153)	7,073	7,788	8,275	8,926	9,615
Rectum (154)	3,715	4,171	4,242	4,407	4,806
Pancreas (157)	2,166	2,776	2,849	2,764	2,541
Larynx (161)	775	837	1,091	1,131	1,308
Trachea, bronchus and lung (162)	17,047	19,376	21,083	20,426	20,851
Malignant melanoma (172)	762	1,167	1,580	2,187	2,546
Breast (174)	9,753	10,722	11,597	12,481	14,449
Cervix uteri (180)	1,515	1,936	2,058	2,128	1,859
Corpus uteri (182)	1,153	1,307	1,530	1,515	1,518
Ovary (183)	1,443	1,984	2,311	2,473	2,508
Prostate (185)	2,546	3,861	4,694	5,648	7,151
Testis (186)	409	514	608	727	844
Bladder (188)	3,027	4,608	5,235	5,706	6,063
Kidney (189)	1,418	1,516	1,860	1,989	2,251
Brain and other CNS (191+192)	1,000	1,265	1,384	1,310	1,515
Thyroid (193)	382	445	452	443	508
Non-Hodgkin lymphoma (200+202)	1,492	2,005	2,433	2,956	3,323
Hodgkin's disease (201)	696	665	691	602	631
Multiple myeloma (203)	785	1,029	1,116	1,228	1,338
Leukaemia (204-208)	1,459	1,726	2,043	2,072	2,138
All malignant neoplasms¹	74,114	87,960	96,532	101,520	109,052

¹ ICD-9 140-208 excluding non-melanoma skin (ICD-9 173)

In the most recent time period, survival at five years after diagnosis varied from under 4% (for patients with pancreatic cancer) to over 90% (for patients with testicular cancer; Figure 3.1). Survival was lowest in patients with cancers which often present at an advanced stage and are less amenable to treatment (examples being pancreatic, lung and oesophageal

cancers). Survival tended to be better for cancers for which patients are more likely to present at an early stage (for example, cancers of the corpus uteri, bladder and thyroid, and malignant melanoma of the skin), for cancers which can be detected early by screening (for example, breast cancer), and cancers for which there have been major advances in treatment (for example, cancer of the testis and Hodgkin's disease). For many cancers, the survival rate five years after diagnosis was over 50%. These include malignant melanoma of the skin, cancers of testis, corpus uteri, breast, bladder, thyroid, cervix uteri and larynx, and Hodgkin's disease, which together account for 27% of malignancies.

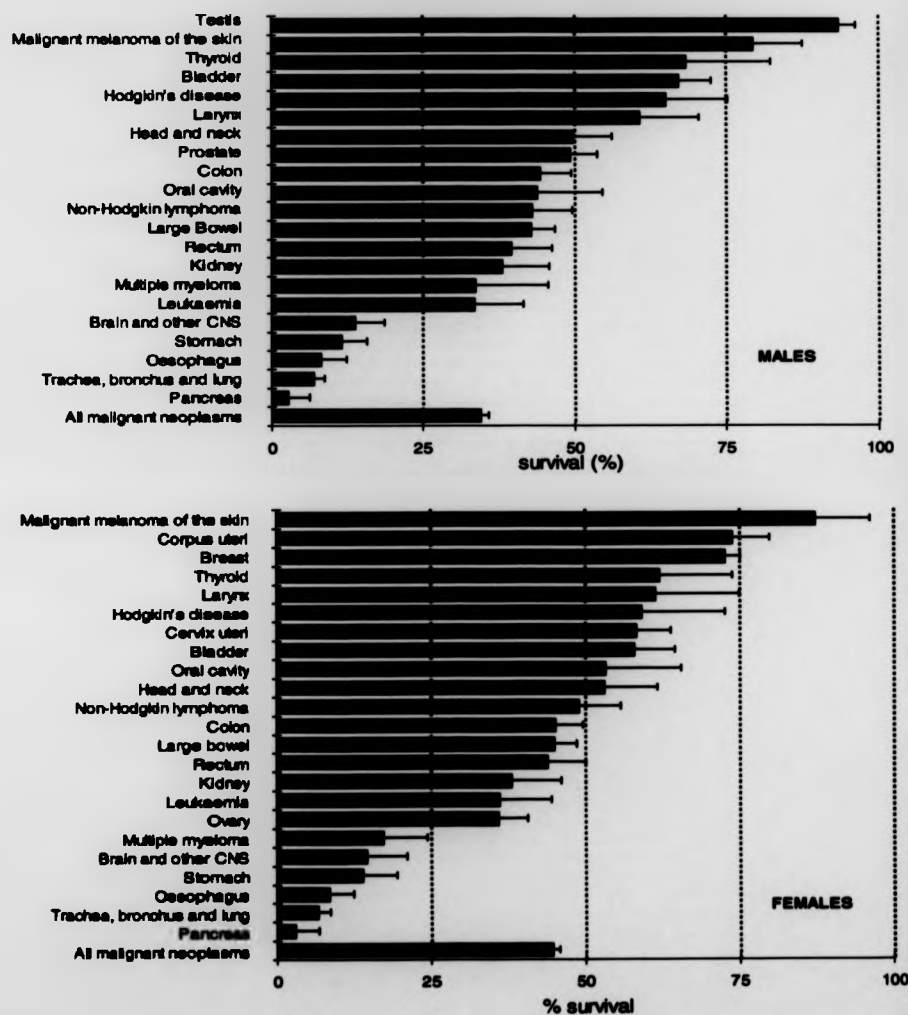
Survival by age

A patient's prognosis after a diagnosis of cancer is highly dependent on age; an individual's risk of dying from a particular cancer once diagnosed tends to increase with age, as does their risk of dying from another cause. Even after adjustment for age-specific competing risks of death, however, using relative survival, survival was generally better in younger patients (Table 3.3). This could be due to better general health, earlier diagnosis or better availability and effectiveness of treatment.

Survival was rarely similar across the age groups, occurring only for patients aged under 85 with large bowel cancer or malignant melanoma of the skin in males. Large variations in survival between age groups were seen for many cancers, in particular thyroid and brain cancers, non-Hodgkin lymphomas, Hodgkin's disease, multiple myeloma, and genitourinary cancers in females. Some of the estimates for the youngest age group were, however, based on very few cases, as indicated by their large confidence intervals.

Survival was low in the youngest patients with laryngeal, breast and prostate cancers, and bladder and multiple myeloma in females. The low rates for laryngeal cancer and multiple myeloma in the youngest age group are again based on very few cases. Young females with bladder cancer also comprise a small patient group, however survival from bladder cancer was lower in females than males in all age groups.

Figure 3.1: Patients diagnosed with cancer in Scotland during 1991-95: five-year relative survival¹ (with 95% confidence intervals), by cancer² and sex



¹ These rates are directly standardised to the world standard cancer patient population.

² For some cancers (testis, brain and other CNS, thyroid and Hodgkin's disease in males; larynx and Hodgkin's disease in females) there were less than 9 cases in the 85-99 age group in any time period. For these sites the standardised rate is based on the age group 15-74.

The pattern for breast cancer is unusual with low survival in younger women, followed by a peak in menopausal women, and decreasing survival in older women. This has been reported elsewhere⁴, and may be related to differences in tumour biology in pre- and post-menopausal women¹⁰⁷. Higher survival seen around menopause could be because lower levels of circulating sex hormones may result in reduced stimulation of tumour cell growth.

Low survival for prostate cancer in men under 60 may also be due to differences in tumour biology¹⁰⁸. Prostate-specific antigen (PSA) testing became widely used in Scotland in 1991 causing a steep increase in incidence between 1992 and 1993. The extent to which this increase represents the early diagnosis of tumours which would eventually cause symptoms or be life-threatening, or detection of latent disease which would never have become symptomatic, is not yet clear. Improvements in survival seen in older men in the 1990s are probably an artefact of the increase in PSA testing, and would not be as likely to be seen in the younger men¹⁰⁹.

Survival by sex

For 'all malignant neoplasms', the survival at one year after diagnosis increased from 36% during 1971-75 to 52% during 1991-95 for males, and from 51% to 61% for females. Survival at five years after diagnosis improved by around 12% for both sexes. The smaller improvement at one year for females than males is a reflection of the comparatively small improvement over the period for survival from breast and gynaecological cancers, rather than because cancer survival has improved more in males than females for specific cancers. These cancers contribute a large proportion (37%) of the cancers in females, for which survival is already relatively high.

The main reasons for the lower overall survival in males than females is the higher proportion of males with lung cancer (25% of male cancers compared to 13% of female) which has a very poor prognosis, and because women have a higher proportion of the cancers which have a good prognosis. Two in 5 women have cancers with an average five-year relative survival rate of over 50%, compared to only 1 in 7 men (Figure 3.2).

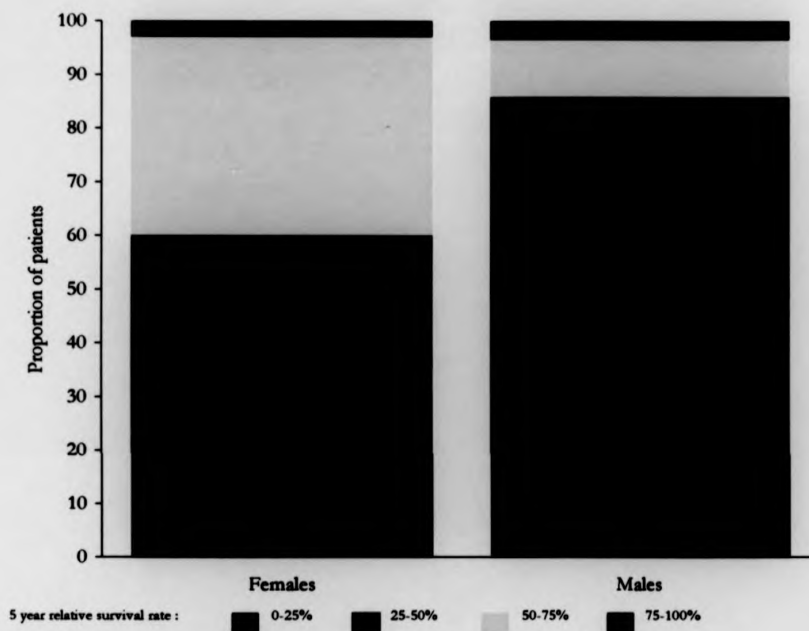
Table 3.3: Patients diagnosed with cancer in Scotland during 1991-95: five-year relative survival (with 95% confidence intervals shown for youngest and oldest age group) by cancer, sex and age group¹

Cancer	Sex	15-44	45-54	55-64	65-74	75-84 ²	85-99 ²
Oral cavity	M	53.5 (39.5, 65.7)	41.6	44.6	40.0	43.5	30.0 (4.6, 62.6)
	F	70.9 (46.2, 85.8)	54.6	62.7	44.8	40.4	18.8 (6.3, 36.4)
Head and neck	M	56.8 (48.3, 64.3)	49.8	51.1	47.5	44.9	44.5 (20.4, 66.2)
	F	64.5 (49.4, 76.1)	58.7	56.0	47.4	45.9	27.0 (14.0, 41.9)
Oesophagus	M	19.5 (9.6, 32.0)	11.0	9.8	7.0	2.2	0.2 (0.0, 2.5)
	F	0.0 (0.0, 0.0)	14.1	11.2	9.0	7.1	0.8 (0.1, 4.2)
Stomach	M	19.4 (11.1, 29.4)	17.4	12.9	10.9	6.9	1.5 (0.2, 6.5)
	F	23.2 (11.7, 36.9)	18.9	13.8	15.1	9.7	2.1 (0.8, 4.6)
Large bowel	M	46.6 (39.7, 53.2)	45.9	47.0	46.4	42.6	27.5 (19.7, 35.8)
	F	50.8 (43.2, 57.9)	50.2	50.8	49.5	42.5	28.9 (24.0, 34.0)
Colon	M	48.5 (39.9, 56.5)	45.4	48.7	46.9	44.0	31.9 (22.0, 42.2)
	F	48.3 (38.6, 57.3)	49.0	48.8	50.6	44.3	30.3 (24.5, 36.3)
Rectum	M	43.7 (32.2, 54.6)	46.6	44.6	45.7	39.8	15.6 (6.4, 28.5)
	F	55.1 (42.6, 65.9)	52.9	55.2	46.7	37.7	23.8 (15.7, 32.8)
Pancreas	M	9.7 (2.6, 22.7)	2.9	4.3	1.5	1.0	0.4 (0.0, 2.5)
	F	5.4 (0.5, 20.1)	3.4	4.1	3.6	1.1	0.8 (0.1, 3.0)
Larynx	M	67.5 (46.9, 81.5)	69.6	63.7	59.9	47.7	45.4 (7.8, 78.3)
	F	56.8 (14.1, 85.0)	82.2	55.7	52.6	42.2	-
Trachea, bronchus and lung	M	17.4 (11.9, 23.8)	11.1	8.5	5.5	2.8	2.3 (1.1, 4.3)
	F	17.7 (11.2, 25.4)	9.0	9.2	4.7	2.3	2.7 (1.2, 5.1)
Malignant melanoma	M	86.0 (80.8, 89.9)	75.9	80.9	77.3	83.4	56.1 (15.9, 83.4)
	F	92.4 (89.5, 94.6)	92.1	93.7	87.9	76.5	62.4 (33.3, 81.7)
Breast	F	76.0 (73.8, 78.0)	79.8	80.4	71.0	60.7	45.8 (39.1, 52.2)
Cervix uteri	F	80.3 (77.1, 83.0)	65.8	53.7	42.2	25.1	4.7 (0.5, 16.8)
Corpus uteri	F	85.3 (73.3, 92.2)	87.7	80.0	70.3	62.5	22.7 (8.7, 40.6)
Ovary	F	66.6 (59.5, 72.8)	39.5	32.1	19.7	13.7	5.1 (1.3, 13.2)
Prostate	M	-	45.1	65.8	58.3	51.0	36.4 (28.8, 44.1)
Testis	M	96.0 (94.2, 97.3)	88.5	82.8	52.2	-	-
Bladder	M	87.3 (79.3, 92.4)	81.5	75.2	70.7	60.9	42.9 (29.0, 56.1)
	F	75.0 (58.4, 85.8)	80.1	72.4	65.3	46.5	26.9 (16.8, 38.0)
Kidney	M	48.7 (36.4, 59.9)	48.0	44.4	38.2	25.9	15.4 (5.2, 30.5)
	F	62.8 (48.0, 74.4)	55.0	38.0	35.8	27.0	8.1 (2.8, 17.2)
Brain and other CNS	M	42.5 (35.2, 49.6)	12.9	3.0	4.6	4.0	-
	F	59.0 (50.2, 66.8)	19.6	5.1	1.1	5.4	6.9 (0.5, 26.4)
Thyroid	M	89.1 (72.1, 96.0)	79.1	74.7	39.7	31.2	-
	F	97.8 (93.1, 99.3)	93.8	73.3	56.6	30.1	8.4 (0.6, 30.7)
Non-Hodgkin lymphoma	M	63.8 (57.4, 69.5)	56.7	47.6	32.5	21.5	8.0 (1.2, 23.7)
	F	65.6 (56.7, 73.2)	66.6	54.3	40.8	28.1	15.1 (6.9, 26.2)
Hodgkin's disease	M	88.4 (82.8, 92.2)	74.9	63.9	25.1	26.9	-
	F	84.7 (77.1, 89.9)	56.2	45.0	39.7	36.2	-
Multiple myeloma	M	76.1 (42.4, 91.7)	28.3	17.7	19.8	14.8	10.0 (0.9, 32.5)
	F	0.0 (0.0, 0.0)	39.1	29.3	19.0	15.1	7.9 (1.6, 20.7)
Leukaemia	M	46.4 (37.6, 54.8)	32.0	37.4	27.5	20.8	11.5 (3.2, 25.7)
	F	45.7 (35.9, 54.9)	41.4	44.4	29.8	21.7	14.6 (7.0, 24.8)
All malignant neoplasms ¹	M	63.7 (61.9, 67.4)	36.8	32.2	28.6	25.0	18.0 (15.6, 20.6)
	F	72.5 (71.1, 73.8)	61.9	51.3	34.8	26.7	18.1 (16.4, 19.9)

¹ It was not possible to calculate survival rates for some cancers because of small numbers of cases.

² ICD-9 140-208 excluding non-melanoma skin cancer (ICD-9 173)

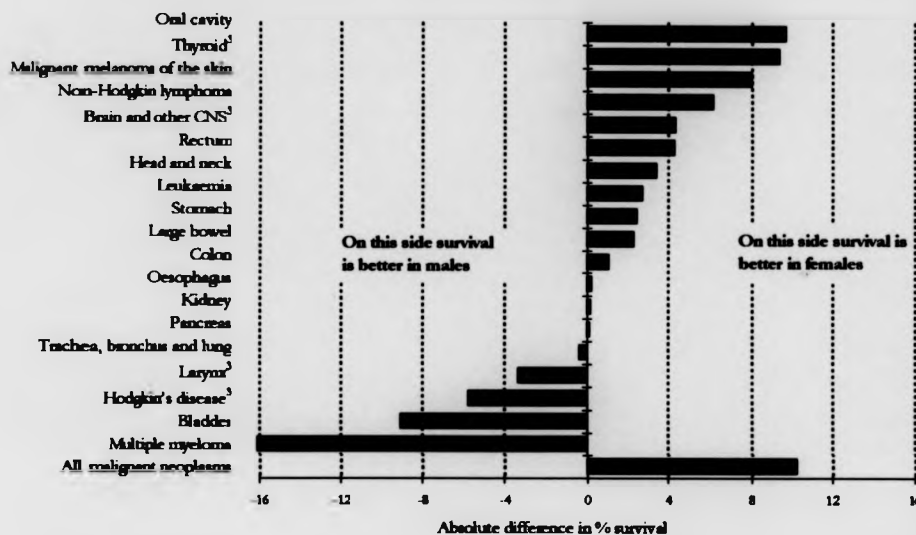
Figure 3.2: Distribution of cancer patients by range of five-year survival¹, by sex, Scotland, ages 15-99, patients diagnosed 1991-95



¹ Directly standardised to the world standard cancer patient population

For many cancers, survival prospects differed between males and females, with females generally surviving longer (Figure 3.3). Cancers where the difference was comparatively large included oral cavity and thyroid cancers, malignant melanoma of the skin, and non-Hodgkin lymphomas, for all of which females had better survival than males; and multiple myeloma, bladder cancer and Hodgkin's disease, where males had a higher survival than females. The apparently poorer survival for females with multiple myeloma is completely artefactual due to the large weight given to the youngest age group (by the world standard cancer population; see Appendix 1.2) to an unstable estimate based on very few cases. The better survival for males with Hodgkin's disease is also compounded by this problem, as male survival is actually poorer in all age groups except the 55-64 year olds. The higher survival for males with laryngeal cancer may also be affected by this problem (small number of cases for females), although there is some evidence of a real survival advantage for males in the older age groups.

Figure 3.3: Patients diagnosed with cancer in Scotland during 1991-95: absolute difference¹ in five-year relative survival² by cancer: males compared to females



¹ Absolute differences in survival between males and females have been shown, for example, the % survival for thyroid cancer was 77.6% in females and 68.2% in males, which by subtraction gives a difference of 9.4%.

² These rates are directly standardised to the world standard cancer patient population.

³ For these sites the comparison was made using standardised rates for the age group 15-74, because there were less than 9 cases in the 85-99 age group either for males or for females.

A multivariate Cox proportional hazards regression analysis³⁹ was performed to investigate the apparent higher survival in males with bladder cancer. When sex alone was included in the model a decreased relative risk of death was observed for males compared to females (RR=0.87; $p<0.001$). However, when age (5-year bands) and morphological type (M8120, M8130, M8010, M8070 and other) were added to the model there was no longer a significant difference in the relative risk of death between the sexes (RR=1.01; $p=0.84$).

Survival by calendar period

For the majority of cancers, survival at one year and five years after diagnosis improved over the period surveyed (Tables 3.4 and 3.5). The largest improvements were seen for large bowel cancers, lympho-haematopoietic malignancies (probably due to the development and implementation of increasingly effective therapies), malignant melanoma of the skin, kidney

and thyroid cancers. Broadly similar findings are seen in cancer survival in England and Wales⁴.

Improvements in survival at five years after diagnosis were generally smaller than those seen at one year indicating that although survival is improving, because of earlier diagnosis and/or improved treatment, the majority of cancer patients are not being 'cured'. Large sustained improvements in survival at five years after diagnosis were seen for malignant melanoma of the skin, large bowel cancers, Hodgkin's disease, leukaemia, and breast, testicular and thyroid cancers. For some cancers the absolute improvement in survival was small, but it represented a large proportional gain. These included oesophageal cancer in males (proportionate improvement of 13%) and stomach cancer (8% in males and 10% in females). No real improvements in survival were seen for lung, pancreatic or laryngeal cancer in males, or cervical cancers.

Survival declined over the period in cancers of the head and neck in males, due to a large decrease in the proportion of lip tumours (22% of all head and neck cancers during 1971-75 to 8% during 1991-95). Lip tumours have a very favourable prognosis, with 91% patients still alive at five years after diagnosis, compared to other sites in the head and neck whose survival at five years after diagnosis ranges from 20% (hypopharynx) to around 60% (larynx and salivary glands). The proportion of lip tumours in females increased slightly over the same period (from 5% to 7%).

The cancers with the largest improvements in survival over time are now discussed.

Malignant melanoma of the skin

The largest absolute improvements in survival at five years after diagnosis over the period 1971 to 1995 were seen for malignant melanoma of the skin (31% in males and 20% in females). This improvement was sustained up to ten years after diagnosis, and so suggests that increasingly more patients are being cured of cancer. Incidence rates have increased dramatically for both sexes over recent years, which is thought to be due, at least in part, to a major public health education programme.

Tumour thickness of cases diagnosed in the West of Scotland was significantly reduced following a campaign to promote early reporting¹¹⁰. Prognosis is directly related to tumour

thickness at diagnosis but the survival improvement seems to be only partly explained by an increasing proportion of thinner tumours¹¹¹. The improvement in survival is seen in both sexes and in all age groups.

Hodgkin's disease

For Hodgkin's disease (HD) there are also large sustained improvements in survival since the early 1970s (15% in males and 16% in females). Incidence of HD is higher in men than women across all age groups. Survival decreases with increasing age but has increased over time within each age group. Due to improvements in diagnostic techniques and changes in the way lymphomas are classified, some cases that would have previously been recorded as HD are now recorded as non-Hodgkin's lymphoma (NHL) which may have affected the survival estimates. However, there have been major improvements in treatment using combination chemotherapy and radiotherapy¹¹² over the period, and these appear more likely to be the reason for the improvement.

Breast cancer

The overall improvement in survival from breast cancer (16% at five years) has been occurring over the whole time period (1971-1995), but with a larger increase in the most recent time period. The incidence of breast cancer has also been increasing over the whole time period, with a very large increase following the introduction of the national breast screening programme in 1988, and it is now returning to levels similar to expected from the underlying incidence trends, but with improved prognostic characteristics¹¹³. In any breast screening programme the survival benefits will be seen very soon after screening begins, but these are difficult to interpret until the prevalent round of screening is completed. This is because the initial screening round will pick up some very slow-growing tumours that may never have presented clinically during the patient's lifetime (length bias).

Table 3.4: Relative survival¹ (%) at one year after diagnosis (with 95% confidence intervals) by cancer and sex, Scotland, ages 15-99, patients diagnosed 1971-95

Cancer	1971-75	1981-85	1991-95
Males			
Oral cancer	64.2 (48.2, 76.1)	71.8 (60.3, 80.4)	72.4 (62.5, 79.9)
Head and neck	77.2 (70.8, 82.2)	78.0 (72.6, 82.4)	76.5 (71.3, 80.7)
Oesophagus	14.5 (9.6, 20.9)	20.1 (15.0, 25.7)	29.0 (23.6, 34.5)
Stomach	15.2 (12.2, 18.5)	22.9 (19.0, 27.0)	30.0 (25.3, 34.9)
Large bowel	43.7 (39.8, 47.5)	53.5 (49.8, 57.0)	64.7 (61.4, 67.7)
Colon	39.9 (35.0, 44.7)	51.3 (46.7, 55.7)	63.1 (58.9, 66.9)
Rectum	49.0 (42.6, 55.0)	57.2 (50.8, 62.9)	67.1 (61.7, 71.8)
Pancreas	7.1 (4.3, 11.1)	9.2 (5.7, 13.6)	10.1 (6.6, 14.8)
Larynx	76.0 (66.4, 81.7)	82.4 (73.1, 88.9)	85.1 (76.1, 90.5)
Trachea, bronchus and lung	16.2 (14.6, 18.0)	18.3 (16.6, 20.1)	21.2 (19.2, 23.2)
Malignant melanoma	75.5 (58.2, 86.6)	87.3 (72.1, 92.8)	93.7 (86.0, 97.1)
Prostate	63.3 (58.0, 68.0)	70.0 (66.0, 73.5)	75.2 (72.3, 77.7)
Testis ²	81.1 (73.6, 86.3)	94.3 (89.1, 96.8)	96.3 (92.5, 98.1)
Bladder	69.6 (63.0, 75.1)	77.0 (72.3, 80.9)	82.4 (78.6, 85.4)
Kidney	41.6 (33.7, 49.5)	45.4 (36.8, 53.7)	56.7 (49.5, 63.3)
Brain and other CNS ²	21.6 (15.9, 28.1)	23.1 (18.0, 28.8)	33.5 (27.7, 39.4)
Thyroid ²	63.1 (37.5, 79.2)	46.9 (29.2, 59.2)	79.5 (58.2, 89.9)
Non-Hodgkin lymphoma	46.7 (37.8, 56.1)	52.1 (45.3, 58.9)	63.3 (57.1, 68.9)
Hodgkin's disease ²	67.1 (56.0, 76.0)	73.3 (60.8, 82.6)	77.5 (65.8, 85.6)
Multiple myeloma	43.6 (29.6, 57.2)	60.6 (45.8, 69.7)	67.8 (50.5, 75.9)
Leukaemia	35.8 (27.6, 44.2)	50.9 (42.9, 58.4)	59.6 (51.8, 66.4)
All malignant neoplasms ³	35.3 (34.1, 36.9)	43.4 (42.2, 44.6)	52.2 (51.1, 53.4)
Females			
Oral cancer	56.6 (43.2, 65.9)	77.3 (61.7, 86.1)	72.7 (59.6, 81.8)
Head and neck	66.5 (57.2, 74.2)	74.6 (66.8, 80.5)	74.7 (67.0, 80.6)
Oesophagus	23.0 (15.3, 31.4)	25.2 (17.3, 33.3)	24.4 (19.6, 29.5)
Stomach	17.4 (13.3, 21.8)	24.7 (19.9, 29.7)	30.0 (23.7, 36.3)
Large bowel	44.8 (41.6, 48.0)	55.2 (52.0, 58.2)	65.4 (62.4, 68.2)
Colon	42.7 (38.9, 46.4)	53.5 (49.7, 57.1)	64.2 (60.5, 67.6)
Rectum	50.2 (43.6, 56.3)	58.8 (53.0, 63.9)	68.1 (62.5, 72.9)
Pancreas	9.0 (5.1, 14.0)	10.2 (6.5, 14.9)	9.7 (5.8, 15.0)
Larynx ²	76.4 (57.3, 87.2)	83.0 (64.1, 91.4)	88.3 (62.5, 78.6)
Trachea, bronchus and lung	14.5 (12.1, 17.4)	17.9 (15.5, 20.4)	21.7 (19.2, 24.2)
Malignant melanoma	89.0 (75.8, 94.3)	94.0 (87.6, 97.1)	97.0 (92.0, 98.8)
Breast	84.3 (82.2, 86.1)	87.5 (85.8, 88.9)	91.2 (89.9, 92.3)
Cervix uteri	75.3 (70.0, 80.1)	75.2 (70.6, 79.3)	79.7 (74.7, 83.8)
Corpus uteri	81.9 (74.3, 87.5)	83.9 (78.3, 87.7)	87.0 (81.7, 90.6)
Ovary	49.3 (43.0, 55.3)	54.2 (49.6, 58.5)	62.1 (57.5, 66.2)
Bladder	57.4 (48.8, 64.8)	66.9 (60.5, 72.1)	72.4 (66.6, 77.0)
Kidney	38.2 (28.1, 48.4)	44.5 (35.0, 53.3)	53.3 (44.9, 60.8)
Brain and other CNS	17.4 (12.3, 24.7)	20.7 (14.9, 28.4)	26.6 (20.4, 33.9)
Thyroid	53.9 (41.7, 63.7)	65.5 (52.6, 75.6)	72.3 (59.3, 81.8)
Non-Hodgkin lymphoma	53.0 (43.4, 61.7)	62.7 (55.9, 68.5)	66.7 (60.6, 71.9)
Hodgkin's disease ²	67.2 (55.3, 76.7)	77.1 (64.0, 85.4)	79.9 (65.1, 88.4)
Multiple myeloma	30.5 (22.2, 38.3)	42.7 (34.6, 49.6)	46.5 (39.3, 52.1)
Leukaemia	38.8 (29.5, 48.1)	47.5 (38.7, 55.6)	57.1 (48.5, 64.5)
All malignant neoplasms ³	51.3 (50.0, 52.5)	55.4 (54.3, 56.4)	61.1 (60.2, 62.1)

¹ These rates are directly standardised to the world standard cancer patient population.

² These rates are standardised for the age group 15-74, rather than 15-99 because of small numbers in the older age groups.

³ ICD-9 140-208 excluding non-melanoma skin (ICD-9 173).

Table 3.5: Relative survival¹ (%) at five years after diagnosis (with 95% confidence intervals) by cancer and sex, Scotland, ages 15-99, patients diagnosed 1971-95

Cancer	1971-75	1981-85	1991-95
Males			
Oral cancer	45.5 (28.8, 60.7)	44.5 (33.0, 56.1)	43.8 (32.6, 54.7)
Head and neck	59.9 (51.3, 67.3)	56.9 (49.6, 63.7)	49.9 (43.0, 56.3)
Oesophagus	3.2 (1.4, 7.5)	4.9 (2.5, 9.1)	8.1 (5.0, 12.4)
Stomach	5.8 (3.9, 8.3)	8.2 (5.7, 11.5)	11.5 (8.1, 15.8)
Large bowel	25.7 (21.9, 30.0)	33.3 (29.2, 37.7)	42.7 (38.5, 46.9)
Colon	26.1 (21.1, 31.6)	33.7 (28.5, 39.0)	44.2 (38.9, 49.5)
Rectum	24.4 (18.9, 31.2)	32.1 (25.5, 39.2)	39.5 (33.0, 46.3)
Pancreas	3.0 (1.2, 6.3)	2.8 (1.1, 6.2)	2.8 (1.0, 6.2)
Larynx	58.4 (45.8, 68.2)	63.2 (51.9, 73.2)	60.6 (48.9, 70.5)
Trachea, bronchus and lung	6.2 (5.0, 7.7)	5.5 (4.5, 6.7)	6.9 (5.6, 8.5)
Malignant melanoma	48.0 (30.0, 65.2)	57.6 (45.0, 69.4)	79.4 (66.9, 87.4)
Prostate	36.4 (29.5, 43.8)	39.3 (33.8, 44.9)	49.3 (44.7, 53.9)
Testis ²	67.5 (59.3, 74.2)	87.3 (81.1, 91.1)	93.5 (89.1, 96.2)
Bladder	54.0 (44.7, 62.3)	58.9 (52.0, 65.2)	67.0 (60.9, 72.5)
Kidney	26.7 (19.3, 35.3)	27.9 (20.9, 37.1)	37.8 (30.2, 45.8)
Brain and other CNS ²	11.1 (7.0, 16.5)	10.4 (6.9, 15.0)	13.7 (9.9, 18.7)
Thyroid ²	52.2 (28.5, 70.5)	37.1 (20.1, 51.8)	68.2 (46.0, 82.3)
Non-Hodgkin lymphoma	30.7 (22.5, 40.5)	33.7 (27.7, 40.7)	42.9 (36.6, 49.8)
Hodgkin's disease ²	49.6 (38.9, 60.0)	56.5 (43.5, 68.5)	64.9 (52.4, 75.3)
Multiple myeloma	18.3 (8.9, 31.1)	22.1 (11.0, 34.7)	33.4 (18.6, 45.6)
Leukaemia	14.3 (8.9, 20.9)	23.3 (17.0, 30.7)	33.3 (25.6, 41.5)
All malignant neoplasms ³	21.6 (20.2, 23.1)	26.4 (25.2, 27.7)	34.4 (33.1, 35.7)
Females			
Oral cancer	37.4 (23.5, 50.3)	57.0 (40.5, 69.5)	53.5 (39.1, 65.5)
Head and neck	48.9 (38.9, 58.3)	57.3 (48.0, 65.2)	53.3 (44.0, 61.7)
Oesophagus	8.5 (4.1, 15.4)	7.8 (3.7, 14.4)	8.3 (5.2, 12.5)
Stomach	6.7 (4.3, 10.0)	9.8 (6.5, 13.8)	14.0 (9.2, 19.6)
Large bowel	27.4 (24.1, 30.9)	34.1 (30.7, 37.5)	45.0 (41.2, 48.7)
Colon	27.5 (23.7, 31.5)	34.8 (30.8, 38.9)	45.3 (40.7, 49.7)
Rectum	26.8 (20.9, 33.5)	31.9 (26.2, 37.9)	43.8 (37.1, 50.3)
Pancreas	4.9 (2.1, 9.1)	3.1 (1.2, 6.6)	2.9 (1.1, 6.8)
Larynx ²	50.8 (31.7, 66.2)	63.0 (43.1, 75.7)	61.3 (42.2, 74.9)
Trachea, bronchus and lung	5.7 (4.2, 7.5)	5.7 (4.3, 7.5)	6.6 (5.0, 8.5)
Malignant melanoma	67.6 (53.7, 78.7)	75.1 (66.5, 82.4)	87.5 (79.5, 92.6)
Breast	56.8 (53.7, 59.8)	62.8 (60.1, 65.3)	72.8 (70.4, 75.1)
Cervix uteri	57.5 (51.6, 63.5)	52.6 (47.6, 57.6)	58.3 (52.8, 63.8)
Corpus uteri	68.3 (59.0, 76.5)	69.4 (62.1, 75.6)	73.9 (66.5, 80.0)
Ovary	32.0 (26.3, 38.3)	32.7 (28.2, 37.4)	35.9 (31.1, 40.7)
Bladder	46.1 (36.4, 55.6)	52.1 (44.7, 59.1)	58.1 (50.6, 64.6)
Kidney	24.3 (16.5, 33.6)	28.4 (20.0, 37.5)	38.0 (29.6, 46.3)
Brain and other CNS	8.9 (4.9, 15.6)	12.5 (7.8, 19.6)	14.6 (10.2, 21.4)
Thyroid	46.1 (34.3, 56.2)	55.5 (43.6, 66.3)	62.0 (48.5, 73.9)
Non-Hodgkin lymphoma	37.8 (28.4, 47.8)	43.7 (36.4, 50.9)	49.1 (42.1, 55.8)
Hodgkin's disease ²	43.2 (31.8, 54.6)	61.3 (47.6, 72.5)	59.2 (43.3, 72.8)
Multiple myeloma	11.9 (6.7, 19.2)	16.4 (10.6, 23.5)	17.4 (11.2, 24.5)
Leukaemia	17.3 (10.7, 25.9)	24.8 (17.5, 32.9)	36.0 (27.4, 44.6)
All malignant neoplasms ³	34.0 (32.6, 35.4)	37.3 (36.2, 38.5)	44.6 (43.5, 45.8)

¹ These rates are directly standardised to the world standard cancer patient population.

² These rates are standardised for the age group 15-74, rather than 15-99 because of small numbers in the older age groups.

³ ICD-9 140-208 excluding non-melanoma skin (ICD-9 173).

Another issue that complicates breast cancer survival estimates is 'lead time', where early diagnosis increases observed survival times without necessarily preventing or postponing death. The improvements in survival from breast cancer in Scotland are even larger at five years after diagnosis than at one year after diagnosis. The introduction and increasing use of adjuvant systemic therapy and improvements in the management of breast cancer patients are both likely to be playing an important role. That the improvements are seen across all age bands (with increases of 7% for the 15-44 year-olds, 18% at ages 45-54, 24% at ages 55-64, 14% at ages 65-74, 5% at ages 75-84, and 10% at ages 85-99 years), not just those in the screening age range, is evidence that at least some of the survival improvement is real. These issues are discussed in Chapter 5.

Testicular cancer

For testicular cancer, the large improvements in survival since the 1970s (26%) can be wholly attributed to the advent of effective chemotherapy⁴. In the youngest age group (15-44 years), where most (86%) testicular cancers occur, the 5-year relative survival rate is now 96%.

Leukaemia

The improvements in survival since the 1970s for leukaemia (19% in both sexes) are also consistent with known advances in therapy. However, despite these improvements, the long-term survival prospects are still poor, and patients who have survived 5 years after diagnosis, still have only a 60% chance of surviving another 5 years (data not shown).

Large bowel cancer

The improvements in survival since the 1970s for large bowel cancer (17% in males and 18% in females) are seen across all age bands, and for colon cancer the largest improvement is seen for older patients. Improved treatment is the most likely cause of the increase.

Thyroid cancer

The improvements in survival since the 1970s for thyroid cancer (16% in both sexes) are based on an unstable trend due to small numbers. This is highlighted by the large

confidence intervals surrounding the estimates. Some improvement is likely to be real due to a shift towards a less aggressive type of thyroid cancer, papillary carcinomas⁴.

Prostate cancer

Small improvements in survival are observed between all the time periods of analysis; however, the large improvement observed in the most recent period is likely to be a length bias artefact, as a result of the introduction of prostate-specific antigen (PSA) testing. Prostate cancer incidence had been steadily increasing since the 1970's, then a large increase in incidence occurred in the 1990s, largely attributed to the increased detection of small, non-lethal tumours through PSA testing.

Cervical cancer

The lack of improvement in survival over time for cervical cancers may reflect the activity of the cervical screening programme. Cervical screening aims to pick up tumours at a pre-invasive stage, so those diagnosed when actually invasive may be more aggressive tumours, i.e. although the incidence of cervical cancer is declining, the proportion of incident invasive tumours with unfavourable prognosis may be increasing.

Whether gains in survival observed in the recent past are likely to continue in the future depends on why survival has improved. Better treatment is likely to account for all or most of the gains in survival from cancers of the testis and bone, Hodgkin's disease and non-Hodgkin lymphoma, and leukaemia; earlier diagnosis may account for higher survival from melanoma of the skin; while higher survival from breast cancer is probably the result of both earlier diagnosis and better treatment¹⁴, and gains for thyroid cancer are at least partly due to a shift in the type of disease.

Survival by deprivation group

Relative survival at five years after diagnosis among patients diagnosed in Scotland during 1991-95 was 11% higher in females and 12% higher in males in the most affluent group than in the most deprived group (Table 3.6). The largest differences in survival were seen for

leukaemia (17%) and malignant melanoma of the skin (16%) in males, and bladder cancer (19%), Hodgkin's disease (18%), kidney (15%) and cervical (13%) cancers in females. Differences of over 5% were also seen for head and neck (11%), stomach (8%), colon (7%) and laryngeal (7%) cancers, non-Hodgkin lymphoma (8%) and multiple myeloma (7%) in males; and stomach (8%), colon (6%), breast (7%) and ovarian (8%) cancers in females. Caution must be used when interpreting these results, because some of the sex-age-deprivation combinations are based on small numbers of cases that may produce unreliable estimates.

The large difference in survival between affluent and deprived females with bladder cancer was restricted to patients aged over 55 years old. There was a strong survival gradient at five-years after diagnosis across the deprivation groups for the 55-74 year olds, ranging from 82% in the most affluent group (139 patients) to 58% for the most deprived group (223 patients). There was no evidence of a survival gradient in the oldest age group with survival of around 46% for patients in deprivation groups 1-4, but a large decrease in survival for patients in the most deprived group (25%; 161 patients).

The difference observed for Hodgkin's disease in females (ages 15-74) was probably artefactual due to a large difference survival for patients aged 55-74 years, ranging from 70% for the most affluent to 42% for the most deprived group, based on only 12 and 13 cases, respectively.

Despite the large overall difference in survival between the most affluent and deprived women with kidney cancer, there was no clear gradient across the deprivation groups at any age. For 55-74 and 75-99 year-olds, the most affluent women had higher survival than women in the other deprivation groups.

For cervical cancer, the deprivation gradient in five-year survival was clearly defined for women aged under 55 years: 82% for the most affluent (184 women) compared to 71% for the most deprived (277) women. For women aged 55-74 years, survival was higher for those in the most affluent group (63%) than in the other deprivation groups (around 47%). There was no trend across the deprivation groups for older women.

Table 3.6: Difference in five-year relative survival estimates^{1,2} between affluent and deprived groups, Scotland, ages 15-99, patients diagnosed 1991-95

Cancer	Males			Females		
	Affluent	Deprived	Diff	Affluent	Deprived	Diff
Oral cavity	43.6 (25.0, 61.7)	36.7 (23.3, 51.3)	6.9	51.3 (26.1, 71.2)	37.8 (19.6, 57.8)	13.5
Head and neck	53.4 (41.7, 63.6)	42.5 (34.0, 50.6)	10.9	55.3 (39.0, 68.6)	50.8 (38.2, 61.9)	4.6
Oesophagus	10.5 (5.3, 17.5)	5.9 (2.5, 11.8)	4.6	8.3 (2.3, 19.2)	8.4 (3.5, 16.1)	-0.1
Stomach	18.2 (11.4, 26.1)	10.6 (6.2, 16.4)	7.6	18.9 (9.7, 29.9)	10.5 (5.2, 18.8)	8.4
Large bowel	46.7 (40.6, 52.7)	40.9 (34.6, 47.2)	5.8	48.8 (43.2, 54.2)	44.2 (38.0, 50.2)	4.6
Colon	46.6 (39.0, 53.9)	39.2 (31.1, 47.2)	7.4	49.5 (42.8, 55.8)	43.7 (36.5, 50.6)	5.8
Rectum	45.9 (35.6, 55.7)	44.9 (33.9, 55.3)	1.0	46.6 (36.5, 56.0)	44.8 (32.7, 55.8)	1.8
Pancreas ³	2.3 (0.4, 8.0)	1.2 (0.2, 5.2)	1.1	2.0 (0.5, 5.4)	2.3 (0.7, 5.9)	-0.3
Larynx ⁴	61.7 (38.3, 78.0)	55.2 (39.9, 67.5)	6.5	-	-	-
Trachea, bronchus, lung	7.7 (5.3, 10.7)	6.2 (4.7, 8.1)	1.5	5.1 (3.0, 8.2)	5.7 (4.0, 7.8)	-0.6
Malignant melanoma	83.4 (63.0, 92.4)	68.0 (44.6, 83.6)	15.5	89.3 (76.4, 95.1)	84.7 (68.3, 92.9)	4.6
Breast	-	-	-	77.2 (73.6, 80.4)	70.3 (66.1, 74.2)	6.9
Cervix uteri	-	-	-	68.6 (57.9, 77.7)	56.1 (48.0, 64.4)	12.5
Corpus uteri	-	-	-	74.4 (62.3, 83.3)	71.3 (56.7, 81.4)	3.2
Ovary	-	-	-	33.3 (25.8, 41.0)	25.0 (17.6, 33.1)	8.3
Prostate	54.6 (48.3, 60.5)	51.7 (43.7, 59.3)	2.9	-	-	-
Testis ⁵	95.5 (90.9, 97.8)	92.4 (85.7, 96.0)	3.1	-	-	-
Bladder	70.2 (61.9, 76.8)	67.4 (57.4, 75.7)	2.8	66.6 (53.0, 76.6)	47.9 (37.2, 57.2)	18.7
Kidney	40.4 (29.2, 52.0)	35.5 (23.3, 48.5)	4.9	45.3 (30.1, 59.1)	30.2 (17.4, 44.1)	15.0
Brain and other CNS	11.9 (7.8, 21.2)	14.4 (7.0, 27.7)	-2.4	20.0 (12.1, 30.6)	15.6 (9.0, 27.3)	4.4
Thyroid ⁴	-	-	-	-	-	-
Non-Hodgkin lymphoma	46.7 (35.8, 57.0)	38.7 (28.7, 50.3)	8.0	50.5 (39.1, 60.7)	48.4 (35.6, 59.7)	2.1
Hodgkin's disease ⁶	64.3 (45.5, 79.7)	71.6 (50.0, 85.6)	-7.3	82.6 (55.0, 94.2)	64.3 (40.0, 81.4)	18.3
Multiple myeloma ³	27.3 (9.1, 48.4)	20.6 (6.2, 39.6)	6.7	21.7 (10.9, 34.8)	20.5 (10.3, 35.3)	1.2
Leukaemia	38.1 (25.4, 50.6)	21.4 (11.2, 34.6)	16.7	37.4 (24.7, 49.6)	33.7 (20.5, 47.4)	3.7
All other malignancies	16.9 (12.8, 21.5)	11.1 (7.9, 15.0)	5.8	19.6 (15.0, 24.4)	14.8 (11.0, 19.1)	4.8
All malignant neoplasms	40.3 (38.1, 42.4)	27.9 (26.0, 29.7)	12.4	49.5 (47.7, 51.3)	38.6 (36.9, 40.4)	10.9

¹ Standardised (ages 15-54, 55-74, 75-99) to the world standard cancer patient population

² Using deprivation-specific life tables

³ Truncated standardised rate (ages 55-99) for the females

⁴ Too few cases to perform the analysis (larynx - females, thyroid - both sexes)

⁵ Age-specific rate for ages 15-54

⁶ Truncated standardised rate (ages 15-74)

Survival differences for males with leukaemia are difficult to interpret, because there was no evidence of a trend across the deprivation gradient for any of the age groups, but for each age group the most deprived group had much lower survival than the other deprivation groups. Survival for young men in deprivation groups 1-4 was around 42% compared to 28% for the most deprived men. For the 55-74 year-old age group, survival was around 35% for men in deprivation groups 1-4 and 24% in the most deprived men; and for the

oldest age group, survival was around 20% for men in deprivation groups 1-4 compared to 7% for the most deprived men.

For males with malignant melanoma of the skin, the magnitude of the difference between the deprivation groups was partly an artefact of the standardisation procedure, because the estimates in the oldest age group are based on a small number of cases. However, in the other age groups, there was clear evidence of a deprivation gradient; five-year survival for 15-44 year-old men from affluent areas was 82% (129 men), compared to 74% for men in the most deprived areas (60 men), and for 45-74 year-old men from affluent areas survival was 89% (95 men) compared to 67% for men from the most deprived areas (60 men).

Deprivation-specific survival estimates vary depending on the type of survival analysis undertaken. Three methods were compared: (1) relative survival using deprivation-specific life tables, (2) relative survival using general life tables, and (3) cause-specific survival. For 'all malignancies combined' the difference in survival estimates between the most affluent and deprived females at five years after diagnosis was 12.3% using method 1, 14.4% using method 2 and 13.3% using method 3, and between affluent and deprived males was 14.4%, 15.0% and 14.1%, respectively (Table 3.7).

Table 3.7: Comparison of five-year survival rates (with 95% confidence intervals) using (1) relative survival with deprivation-specific life tables (*dep*), (2) relative survival with general life tables (*gen*), and (3) cause-specific survival, Scotland, ages 15-99, patients diagnosed 1991-95, all malignancies combined

Deprivation category	1-year survival			5-year survival		
	Relative (<i>dep</i>)	Relative (<i>gen</i>)	Cause-specific	Relative (<i>dep</i>)	Relative (<i>gen</i>)	Cause-specific
Males						
Affluent	58.3 (57-60)	58.5 (57-60)	64.0 (62-66)	39.6 (38-42)	40.3 (38-42)	51.0 (49-53)
2	54.4 (53-56)	54.4 (53-56)	59.5 (58-61)	36.4 (34-38)	36.3 (34-38)	46.8 (45-49)
3	51.9 (50-54)	51.8 (50-54)	57.2 (55-59)	34.6 (33-37)	34.2 (32-36)	44.9 (43-47)
4	49.7 (48-51)	49.4 (48-51)	55.3 (53-57)	31.7 (30-34)	30.8 (29-33)	43.0 (41-45)
Deprived	43.9 (42-46)	43.5 (42-45)	49.9 (48-52)	27.3 (26-29)	25.9 (24-28)	37.7 (36-40)
Overall	51.4 (51-52)	51.3 (51-52)	57.0 (56-58)	33.7 (33-35)	33.2 (32-34)	44.6 (44-46)
Females						
Affluent	65.3 (64-67)	65.4 (64-67)	69.2 (68-71)	48.8 (47-51)	49.1 (47-51)	56.4 (54-58)
2	62.1 (61-64)	62.1 (61-64)	66.0 (64-67)	45.5 (44-47)	45.6 (44-47)	53.3 (52-55)
3	60.0 (59-62)	60.0 (59-62)	64.5 (63-66)	43.8 (42-46)	43.7 (42-45)	52.1 (50-54)
4	57.5 (56-59)	57.4 (56-59)	61.9 (60-63)	42.3 (41-44)	41.7 (40-43)	50.4 (49-52)
Deprived	54.8 (53-56)	54.6 (53-56)	59.3 (58-61)	37.9 (36-40)	37.0 (35-39)	47.0 (45-49)
Overall	59.9 (59-61)	59.8 (59-61)	64.1 (63-65)	43.6 (43-44)	43.3 (43-44)	51.8 (51-53)

The survival estimates produced by the three methods when specific cancers were analysed were very different for some cancers (data not shown). However, all three methods showed similar trends across the deprivation groups for all cancers. The two relative survival methods produced similar overall survival estimates, and where the estimates did differ (difference of more than 2%), this was because the survival estimates using deprivation-specific life table were higher for the more deprived groups (deprivation categories 4 and 5) than if general life tables were used. This most notably occurred for males in the oldest age group (75-99) for a number of cancers (data not shown).

The cause-specific estimates did not appear to be comparable to the relative survival estimates, with differences in survival of up to 25% for some cancers. Many of the large differences were in the lympho-haematoetic malignancies: for example, for men from deprivation group 3 aged 75-99 diagnosed with leukaemia (75 men) the relative survival estimate was 13% compared to a cause-specific survival estimate of 38%. The cause-specific survival estimates were generally higher than the relative survival estimates at both one and five years after diagnosis. This very probably indicates an under-assigning of deaths to cancer on death certificates, particularly in older patients. However, for patients with malignant melanoma of the skin and large bowel, bladder and prostate cancers, the cause-specific survival estimates were lower than the relative survival estimates. This is difficult to explain, as it seems unlikely that patients with cancer have a better underlying mortality than the general population. For prostate cancer, this may again be an artefact of PSA testing, resulting in over-reporting of prostate cancer as the primary cause of death on death certificates¹¹⁵.

Despite the improvements in survival observed over time in Scotland, there are still large variations in survival between deprivation groups for patients diagnosed during 1991-95 for some cancers, in particular for colon, breast, cervix, ovary, bladder and kidney cancers, and malignant melanoma of the skin. These differences are quantified in Chapter 4.

AVOIDED AND AVOIDABLE DEATHS

Background

There are a number of references to "avoidable mortality" in the literature. The concept was first proposed by Rutstein *et al*¹⁶ and was defined as "mortality wholly or substantially avoidable by adequate medical care". The authors presented lists of causes of death defined as "avoidable" or "partly avoidable", either through prevention or treatment. The "avoidable mortality" list included a number of cancers (ICD-10 codes: C02, C04, C06, C32, C33, C34, C44, C67, C73 and C92). Subsequently, these lists have been used in other studies¹¹⁷⁻¹¹⁹ to investigate the risk of death from avoidable causes in relation to socio-economic status and area of residence. This method relies on the adequacy of the lists, on the reliability of the information recorded on death certificates and the comparability of death certificates between different populations. The method can be used for calculation of avoidable mortality in the population as a whole but cannot be restricted to, for example, a cohort of cancer patients' excess mortality. This has been achieved through retrospective follow-up studies where death is attributed to either the cancer, unrelated causes and avoidable (treatment or care related) causes through the examination of medical records¹²⁰.

The idea of estimating "avoidable mortality" is being increasingly used in Public Health. The government health target of July 1999 stated the aim "to reduce mortality from cancer in people aged under 75 in England by at least 20% by the year 2010 [compared to 1997] - saving up to 100,000 lives"⁴⁷. The extent to which this target is likely to be met can be partly investigated by looking at avoidable mortality, or avoidable deaths.

Population-based methods of estimating "avoidable deaths" - without the problems of creating lists of avoidable illnesses and having to rely on death certificate information - have recently been published. They can be used to look at excess mortality in specific populations of patients e.g. cancer patients. They are based on differences in cancer survival between groups of patients, and are defined as the number of deaths attributable to cancer

that would be avoidable if patients in all groups were to have the same relative survival as that actually observed for patients in the "best" group. This approach can be applied to differences between socio-economic groups, geographic regions or countries. An equivalent question is to ask how many deaths have been avoided through improvements in survival between two time periods, and this can be termed the number of "avoided deaths".

Two methods of calculating "avoidable deaths" have been identified in the literature: one based on a standardisation-type technique⁴ and the other based on a modelling approach³⁵. These methods are presented in detail in the methods section, and the number of cancer deaths that would be avoidable if all socio-economic groups in Scotland had the same survival as the most affluent socio-economic group and the average survival for Europe are presented in the results section. The numbers of cancer deaths that have been avoided due to improvements in survival over time in Scotland are also presented.

These are the only references found in the literature where avoidable deaths are calculated using survival analysis techniques. However, similar methodology has recently been used in a different context - to investigate the reduction in persons being admitted to hospital if personal risk factors could be changed¹²¹. The authors use the term "*What if.....?*" scenarios and their approach is to manipulate regression coefficients calculated in a multivariate logistic regression model. For example, to calculate the predicted probability of hospital admission [what] if their entire cohort had never smoked, the regression coefficient of the 'never smoked' category was assigned to the other categories of the smoking variable (i.e. 'ex-smoker', 'current smoker'), whilst the coefficients of the other predictor variables were unaltered. The resulting predicted probability was then summed to calculate the predicted number of persons admitted to hospital if none of the cohort had ever smoked and this was compared to the number of persons actually admitted to hospital in the cohort.

Data and Methods

Data

Survival variations in Scotland between deprivation groups and over time

Trends in survival for patients diagnosed with cancer in Scotland between 1971 and 1995 and followed up to the end of 1998 have been reported in *Chapter 3*. For the analyses in this

chapter, 5-year relative survival estimates for patients diagnosed during 1971-1995 were extracted by type of cancer, sex, period of diagnosis, age at diagnosis and deprivation category. Deprivation-specific life tables for Scotland were used in the calculation of relative survival. See *Chapters 1, 2 and 3* for a detailed description of the analytic methods for the estimation of the cancer survival trends, data collection and exclusion criteria. For the standardisation analysis, information on numbers of cases and the cumulative relative survival rates at five and ten years after diagnosis was extracted. For the modelling analysis, information on the numbers of cases, number of deaths, interval-specific expected survival rates and interval-specific relative survival rates was extracted for each 6-month follow-up interval up to five years after diagnosis.

Survival in Scotland compared to Europe

The number of avoidable deaths may be calculated as compared to, for example, the "average" survival between societies or to the society with the "best" survival. In this chapter, survival in Scotland has been compared to that in the other countries within Europe using data from the EUROCARE II study⁶. Numbers of cases and five-year relative survival rates for patients diagnosed during 1985-1989 (the most recent period available) were extracted by type of cancer, country, sex and age at diagnosis (15-44, 45-54, 55-64, 65-74, 75-99 years).

The countries included in the EUROCARE II study are:

Austria	Denmark	England	Estonia
Finland	France	Germany	Iceland
Italy	Netherlands	Poland	Scotland
Slovakia	Slovenia	Spain	Sweden
Switzerland			

Methods

The two methods for calculating avoided and avoidable deaths, identified in the literature, are explained below:

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Standardisation Method

The standardisation method⁴ calculates the number of avoided (or avoidable) deaths as the difference between the observed and expected *excess cancer mortality*, where the *excess cancer mortality* is defined as the number of deaths observed within (say) 5 years of diagnosis, over and above the number of deaths that would have occurred if the patients had only experienced the same mortality as that of the corresponding sex and age group of the general population during the same calendar period.

For example, the observed *excess cancer mortality*, for patients diagnosed 1991-95, is estimated by multiplying the complement of the relative survival rate for 1991-95 for each category of sex and age by the corresponding number of patients diagnosed during 1991-95. The excess mortality for each cancer is then the sum of these estimates across all subgroups. The expected *excess cancer mortality* is estimated in a similar fashion, but using the complement of the relative survival rate for patients diagnosed during 1986-90, multiplied by the number of patients diagnosed during 1991-95. This represents the excess deaths that would have been expected among patients diagnosed during 1991-95 if there had been no improvement in relative survival over the previous five years.

The number of avoided deaths in patients diagnosed during 1991-1995 compared to those diagnosed during 1986-90 is, therefore, calculated for each cancer (by i =age, j =sex) as

$$\text{Avoided} = \sum_j N_{1991-95j} (RSR_{1991-95j} - RSR_{1986-90j})$$

where,

$N_{1991-95}$ = Number of patients diagnosed (and in the analysis) during 1991-95

$RSR_{1991-95}$ = Relative survival rate for patients diagnosed during 1991-95

$RSR_{1986-90}$ = Relative survival rate for patients diagnosed during 1986-90

The percentage of avoided deaths is calculated as the number of avoided deaths divided by the expected excess cancer mortality.

The number of avoidable deaths if patients in all groups of society had the same prospects as those in the most affluent group is calculated for each cancer (by i =age, j =sex) as

$$\text{Avoidable} = \sum_{ij} \left(\sum_{k=2}^5 N_{ijk} (RSR_{ijdepcat1} - RSR_{ijk}) \right)$$

where,

k = Deprivation category (2 to 5)

N_k = Number of patients in deprivation category k

$RSR_{depcat1}$ = Relative survival rate for patients in deprivation category 1 (most affluent)

RSR_k = Relative survival rate for patients in deprivation category k

The percentage of avoidable deaths is calculated as the number of avoidable deaths divided by the observed excess cancer mortality summed over the deprivation categories.

Modelling Method

The modelling method³⁵ uses the interval-specific numbers of cases, deaths and expected mortality (calculated from life tables) in a multiple regression model. The total mortality rate (number of deaths divided by person-years at risk) for persons diagnosed with cancer is modelled as the sum of the known baseline mortality (the expected mortality) and the excess mortality due to a diagnosis of cancer.

The excess mortality, v , is assumed to be a multiplicative function of the covariates (e.g. p =period, i =age, j =sex), such that

$$v_{pij} = e^{(\beta_p + \beta_i + \beta_j)}$$

and the annual interval-specific relative survival is

$$RR_p = e^{\beta_p}$$

The magnitude of the expected random variation (s_b^2) can be estimated based on the number of cases and the survival rate. The variance of the true systematic effects (σ_p^2) can therefore be estimated (V) as

$$V = s_b^2 - \overline{V_1} + \overline{V_2}$$

$$\text{where } s_b^2 = \frac{1}{n-1} \sum_{p=1}^n (b_p - \bar{b})^2, \quad \overline{V_1} = \frac{1}{n} \sum_{p=1}^n \text{var}(b_p), \quad \overline{V_2} = \frac{2}{n(n-1)} \sum_{p>s} \text{cov}(b_p, b_s)$$

and n represents the number of time periods (p). The mean of the β s (\bar{b}) is set to zero.

V will be zero or negative if no systematic variation in survival exists and will increase in magnitude as the level of systematic variation increases. Shrinkage estimates (i.e. estimates that are adjusted to remove the effect of random variation) of the relative risk of excess mortality due to cancer for patients diagnosed in time period p , are calculated by shrinking the crude relative risks towards the mean ($RR=1$), such that

$$RR_p^* = \begin{cases} e^{\vartheta \beta_p} & \text{if } V > 0 \\ 1 & \text{otherwise} \end{cases}, \text{ where } \vartheta = \sqrt{\frac{V}{s_b^2}}$$

Finally, the number of cancer deaths in follow-up interval f , age i , and sex j is defined as the number of deaths (calculated from the number of cases (d) and the model-based interval-specific relative survival (r)) minus the number of expected deaths ((p) calculated from life tables), such that

$$C_{ijf} = I_{ijf} p_{ijf}^* (1 - r_{ijf})$$

The number of cancer deaths if there was no variation in survival over time period (or social groups etc.) is calculated as

$$C_{ij}^{new} = i_{ij} p_{ij}^* (1 - r_{ij}^{new})$$

Where $r_{ij}^{new} = e^{-\frac{1}{p_{ij}}}$ and $v_{ij}^{new} = 1.96 \sqrt{\frac{1}{V}} v_{ij}$

and v_{ij} is based on the estimates from a model containing no time period term.

The calculation is based on the lower confidence interval of the shrinkage estimates in order to look at improvements that have been made (i.e. comparing higher estimates to lowest estimate). When looking at avoidable deaths between deprivation groups (i.e. comparing lower estimates to the highest estimate) then the calculation is based on the upper confidence interval which in practical terms means inserting a minus sign in front of the 1.96 in the above equation.

The number of avoided (or avoidable) deaths is then calculated as

$$A = \sum_{ij} C_{ij} - C_{ij}^{new} \quad \left. \vphantom{\sum_{ij}} \right\} \begin{array}{l} \text{if } V > 0 \\ \text{otherwise.} \end{array}$$

$A = 0$

The choice for the model used for each analysis is based on the change in deviance as extra terms are added to the model (compared to the chi-squared distribution). Generally, the smaller s^2 (=deviance/d.f.) represents a better model fit. The significance of the period (or deprivation) term in the chosen model can be similarly investigated by looking at the significance of the difference in deviances between the chosen model and the same model with the period (or deprivation) term omitted. The model-based interval-specific relative survival estimates can be compared to the true relative survival estimates to visually assess model fit.

Choosing the comparison group - "average" or "best"

When comparing survival in Scotland to that in Europe, different scenarios can be considered. We have estimated how many cancer deaths could be avoidable within five years of diagnosis among cancer patients diagnosed in Scotland (based on relative survival estimates for Scotland from Eurocare II) if survival rates for these patients was equivalent to:

- (a) The weighted average cancer survival in Europe
- (b) The "best" cancer survival in Europe

The "weighted average" cancer survival in Europe was calculated by multiplying each countries cancer-, age- and sex-specific relative survival rates by a weight calculated as the totality of cases diagnosed in country *k* divided by the totality of cases diagnosed in all the countries considered (excluding Scotland). These weights were calculated and applied separately for each cancer, age and sex.

The "best" cancer survival in Europe was calculated as the *analysis weighted* average of the relative survival estimates of the three countries with highest cancer-specific age-standardised relative survival estimates (excluding England, Scotland and Switzerland⁴). The cancer-specific (but not age- and sex-specific) weight was calculated as the number of cases analysed in country *k* divided by the number of cases analysed in the three "best" countries. The *cases analysed* weight rather than a *totality of cases* weight was chosen to avoid giving too much weight to estimates based on small numbers (because for some countries the survival estimates are based only on a small area of the country). The weights were applied to the age- and sex-specific relative survival estimates for the three countries.

The three countries with the highest age-standardised relative survival rates are included for each cancer. Austria and Sweden are the two countries which appeared amongst the "best" the most frequently (Table 4.1). For example, Austria was one of the "best" three for 11 of the 22 cancers studied. The majority of countries appearing in the "best" three were only represented by a small proportion of the countries population and so may not be

⁴ Switzerland (based on the Geneva cancer registry data) is excluded from the choice of "best" because of problems identifying dead patients due to a highly transient population

representative of the country. However, their survival estimates still indicate a level of survival that is achievable even if this may not have been achieved countrywide.

Table 4.1: The countries with the highest survival as identified by EUROCare-II⁶, by cancer

Country	Number of cancers ¹	% Coverage of the national population ²
Austria	11	7.8
Denmark	1	100
Estonia	1	100
Finland	5	100
France ³	7	3.0-5.6
Germany	5	1.7
Iceland	7	100
Italy	2	9.7
Netherlands ³	6	5.7-20.5
Slovakia	4	100
Slovenia	1	100
Spain ³	5	9.6-12.9
Sweden	14	17.5

¹ The number of cancer sites for which each country had first, second or third highest age-standardised survival

² The proportion of the national population included in the EUROCare-II data

³ These countries also have specialised cancer registers leading to increased coverage for some cancers

The number of avoidable deaths for the European analysis was calculated for each cancer (by i =age, j =sex) as

$$\text{Avoidable} = \sum_{ij} N_{ij} (RSR_{\text{expected } ij} - RSR_{\text{Scotland } ij})$$

where,

N = Totality of cases diagnosed in Scotland during 1985-89

RSR_{expected} = Eurocare II relative survival rate for the European "weighted average" or "best"

The follow-up interval

The calculation of avoided deaths covers a finite follow-up interval, say five years, and it does not represent the number of deaths avoided due to changes in the effective "cure" of patients over time. Where sustained improvements in survival are seen for cancers with long-term excess cancer mortality (e.g. breast cancer), the number of avoided deaths will

continue to increase as time since diagnosis increases. By contrast, for cancers with very poor survival for which improvements in survival tend to extend life rather than increase the proportion of patients cured (e.g. lung cancer), the number of avoided deaths will decrease with time since diagnosis as the initial survival advantage is lost (see Table 4.2). Ideally, one would measure the number of avoided deaths from diagnosis to the time of cure, which will vary between cancers, and over time.

Table 4.2: The number of avoided deaths within a specific time interval: patients diagnosed in Scotland during 1986-90 with breast and lung cancer

Time since diagnosis	Breast cancer	Lung cancer
1 year	276	176
3 years	701	91
5 years	1,025	83
10 years	1,141	61

The number of cases used in the calculations

It can be argued that the number of cases *included in the analysis* should be used in the calculation of "avoidable deaths" instead of *totality of cases* diagnosed. This is because the main reasons for exclusion of cases from survival analyses are generally if the cancer was not a first primary or if the only information about the cancer was from the death certificate. These cancers are expected to have a poorer than average survival, and therefore it would seem inappropriate to include them in the calculation. Including only the number of cases analysed leads to conservative estimate of the number of avoidable deaths. However, the Eurocare II study population covered only 50% of England (100% of Scotland, 0% of Wales) and so in an analysis of avoidable deaths in England compared to Europe it would be inappropriate to base the number (N) in the avoidable deaths calculation on cases *included in the analysis*. The choice of N can greatly effect the estimated number of "avoidable deaths" and so should be carefully considered and clearly stated when presenting results. It was felt to be appropriate to use number of cases *included in the analysis* for this chapter, as a high proportion of Scottish cases were included in the Eurocare analyses, and the exclusions were for valid reasons as mentioned above.

Variability in the data

When comparing many survival rates – e.g. by cancer, age, sex, period, country or deprivation category – there will be some estimates based on very small numbers which may not be stable. When there are very few cases, or few cases and no deaths, the survival estimates will not be computed. For the standardisation method, when making comparisons over time, the effect of unstable or missing estimates on the final estimates of avoided deaths will be small, as the *N* corresponding to the unstable or missing survival estimates will be, by definition, very small. However, when comparing countries with very different incidence of cancers, particularly over age, this can be more of a problem and should be borne in mind. The modelling technique includes a random variation component to account for these situations, although there are still problems if estimates are missing.

Results and commentary

Avoided deaths

Cancer survival in Scotland has been increasing over time (see Chapter 3). The numbers of deaths that have been avoided within 5 years of diagnosis, due to improvements in survival for cases diagnosed in 1991-95 compared to those diagnosed in 1986-90, was calculated using the both the standardisation and modelling method. The “all malignancies combined” estimate was calculated both from (1) the sum of the individual cancers plus the “other malignancies” group and (2) from an analysis of the whole data set combined. The individual cancers included amounted to 90% of all malignant neoplasms (excluding non-melanoma skin cancer).

In the standardisation analyses the estimated number of avoided deaths was 3 316 (4.6% of cancer deaths that would of occurred) when the individual cancers were summed or 4 276 (5.8%) if the whole data set combined was analysed (Table 4.3). Using the sum of individual cancers should be a more reliable estimate as it takes account of cancer case-mix (changes in the proportion of different cancers, with varying survival, diagnosed). The “other malignancies” group may be confounded by problems of case-mix, but the analysis of this group was not split down further due to the small numbers for individual cancers and because half of this group comprise of cancers of ill-defined primary site, secondary malignancies and unspecified site (ICD9 195-199). The largest numbers of avoided deaths

were seen for cancers of the breast (1 026 deaths avoided), large bowel (824), prostate (466) and bladder (353). Results for England and Wales, based on an analysis of deaths avoided by improvements in survival between 1981-85 and 1986-90, showed the same cancers as having the largest numbers of avoided deaths¹²² with the exception of prostate cancer (but this may be explained by the different time periods studied - the increases in prostate cancer survival in Scotland in the 1990s are likely to be largely an artefact of PSA testing).

Table 4.3: Avoided deaths within five-years of diagnosis due to improvements in survival over time using the standardisation method: patients aged 15-99 diagnosed in Scotland during 1991-95 compared to 1986-90

Cancer	Number of patients	Number of deaths	Number of excess cancer deaths ¹		Avoided	
			Observed	Expected	N	%
Oral cavity	1,261	759	697	731	34	4.6
Oesophagus	3,285	3,055	3,044	3,086	42	1.4
Stomach	4,722	4,250	4,214	4,296	82	1.9
Large bowel	14,421	9,152	7,998	8,822	824	9.3
Colon	9,615	6,069	5,259	5,796	537	9.3
Rectum	4,806	3,083	2,747	3,030	284	9.4
Pancreas	2,541	2,474	2,481	2,481	0	0.0
Larynx	1,302	619	520	530	10	1.8
Lung	20,850	19,670	19,667	19,754	86	0.4
Melanoma	2,542	600	384	432	48	11.2
Breast (females)	14,449	4,874	3,926	4,951	1,026	20.7
Cervix uteri	1,859	751	721	752	31	4.1
Body of the uterus	1,518	520	417	473	56	11.9
Ovary	2,507	1,827	1,813	1,841	28	1.5
Prostate	7,147	4,274	3,281	3,748	466	12.4
Testis	834	60	50	67	17	25.0
Bladder	6,062	2,908	2,117	2,470	353	14.3
Kidney	2,251	1,501	1,417	1,485	68	4.6
Brain and other CNS	1,505	1,260	1,267	1,315	49	3.7
Thyroid	504	135	126	139	13	9.3
Non-Hodgkin's lymphoma	3,319	2,027	1,916	1,965	49	2.5
Hodgkin's disease	618	189	183	223	40	17.8
Multiple myeloma	1,335	1,093	1,080	1,083	3	0.3
Leukaemia	2,129	1,554	1,495	1,538	43	2.8
Other malignancies ²	12,018	10,262	10,249	10,200	-49	0.4
All malignancies ³	108,979	73,814	69,746	74,022	4,276	5.8
All malignancies ⁴	108,979	73,814	69,070	72,386	3,316	4.6

¹ Excess deaths = number of cases \times (1- relative survival rate)

² Including ICD9 140, 142, 146-149, 152, 155, 156, 158, 159, 160, 163, 164, 165, 170, 171, 175, 179, 181, 184, 187, 190 and 194-199

³ Calculated from an analysis of the whole dataset combined (excluding non-melanoma skin cancer)

⁴ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

The *number* of avoided deaths is dependent both on the incidence of the cancer and on the survival gradient itself. It highlights those cancers for which the improvements in survival over time have had the largest impact on total cancer mortality. The *percentage* of avoided deaths highlights those cancers for which there have been the largest improvements in survival, and is not dependent on incidence. The cancers with the largest percentages of avoided deaths are testis (25%), breast (21%), Hodgkin's disease (18%), bladder (14%), prostate (12%), corpus uteri (12%) and malignant melanoma of the skin (11%).

Looking at the numbers of avoided deaths within five years and ten years of diagnosis over the whole time period 1971-1995, the number of avoided deaths within 5 years of diagnosis for "all malignancies combined" increased by a similar amount over each time period (Table 4.4), and the percentage of deaths avoided within 5 years increased from 1% to 5% over the whole period. For almost all cancers a gain was seen within each period compared to the previous period although the magnitude of the gain varied over time (data not shown). The gains 10 years after diagnosis were generally smaller than those seen after 5 years due to the prolonging of life but no cure for a proportion of the patients. The exceptions to this were testicular cancer, thyroid cancer and malignant melanoma of the skin indicating that a sustained and increasing improvement in survival was occurring as time since diagnosis increased for these cancers. For lung cancer, bladder cancer and leukaemia, deaths had been avoided at 5 years after diagnosis but these had disappeared by 10 years after diagnosis. The proportion of deaths avoided within 10 years of diagnosis was also increasing with time, with 3% of deaths avoided within 10 years of diagnosis in patients diagnosed 1986-90 compared to those diagnosed 1981-85, whereas only 1% of deaths were avoided in patients diagnosed 1981-85 due to improvements in survival from 1976-80 (Table 4.4).

Two models were adopted for the regression analysis: model 1 (period, sex and age terms) and model 2 (period, sex, age and an age by follow-up interaction terms). For cancers where the model fit was poor for both models, examination of the relative risk estimates for period by age and sex, led to additional age terms being added in some instances. For some cancers where estimates were based on small numbers of cases, the model fit was improved by reducing the number of follow-up intervals in the analysis. When the estimated variance of the true systematic effects (V) was zero or negative then the number of deaths avoided were assumed to be zero.

Table 4.4: Number and percentage of deaths avoided within 5 and 10 years of diagnosis due to improvements in survival over time using the standardisation method: patients diagnosed in Scotland during 1971-95, each period compared to the previous period¹

Time since diagnosis	Cancer	1976-80		1981-85		1986-90		1991-95	
		N	%	N	%	N	%	N	%
5 years	All malignancies ²	1,147	1.8	2,120	3.0	3,510	4.9	4,276	5.8
	All malignancies ³	729	1.1	1,633	2.3	2,622	3.7	3,316	4.6
10 years	All malignancies ²	924	1.3	1,736	2.3	2,853	3.7	-	-
	All malignancies ³	509	0.7	1,378	1.9	2,189	2.9	-	-

¹ Estimates for 1976-80 are based on improvements since 1971-75, etc

² Calculated from an analysis of the whole dataset combined (excluding non-melanoma skin cancer)

³ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

The total number of cancer deaths was calculated from the model-based relative survival estimates and so varies from the numbers of cancer deaths shown in Table 4.3 for the standardisation method. The estimated number of avoided deaths for "all malignancies combined", calculated as the sum of the individual cancers, was 2 411 (3.9% of cancer deaths that would of occurred; Table 4.5). If the random variation component is not taken into account then the estimate is higher (3 260 deaths avoided; 5.2%). The largest numbers of avoided deaths were generally seen for the cancers where the period term was very significant in the chosen model. The cancers with the largest number of avoided deaths were the same as identified by the standardisation method, including cancers of the breast (738 deaths avoided), large bowel (712), prostate (214) and bladder (257).

Table 4.5: Deaths avoided due to improvements in survival estimated with the modelling method: patients diagnosed in Scotland during 1991-95 compared to 1986-90

Cancer	Sex	Power of age term	Age by follow-up ¹ interaction	Selected model			P-value for period ²	V ³
				Deviance	D.F.	Deviance /D.F.		
Oral cavity	M	2		128.8	95	1.36	0.820	-0.0024
	F	2		115.6	92	1.26	0.770	-0.0119
Oesophagus	M	4	Yes	98.7	91	1.08	0.014	0.0002
	F	3		98.3	94	1.05	0.608	-0.0023
Stomach	M	3	Yes	94.7	92	1.03	0.000	0.0018
	F	4	Yes	131.2	90	1.46	0.104	-0.0027
Colon	M	3	Yes	145.5	89	1.63	0.000	0.0019
	F	3	Yes	198.8	90	2.21	0.000	0.0028
Rectum	M	2	Yes	148	92	1.61	0.002	0.0030
	F	2	Yes	138.3	92	1.50	0.001	0.0036
Pancreas	M	1		119.4	95	1.26	0.760	-0.0034
	F	4		98.7	92	1.07	0.510	-0.0045
Larynx	M	1		95.1	94	1.01	0.720	-0.0033
	F	1	Yes	100.2	95	1.05	0.380	-0.0039
Lung	M	3	Yes	223	92	2.42	0.045	-0.0001
	F	2	Yes	184.7	93	1.99	0.420	-0.0004
Melanoma	M	1		103.3	96	1.08	0.140	0.0044
	F	2		88.1	95	0.93	0.970	-0.0126
Breast	F	2	Yes	400.9	88	4.56	0.000	0.0135
Cervix uteri	F	3	Yes	145	93	1.56	0.500	-0.0010
Body of the uterus	F	2	Yes	115.7	94	1.23	0.050	0.0028
Ovary	F	3	Yes	221.7	89	2.49	0.002	0.0018
Prostate	M	3	Yes	195.1	68	2.87	0.000	0.0017
Testis	M	2		91.2	93	0.98	0.270	-0.0275
Bladder	M	3	Yes	92.8	91	1.02	0.001	0.0086
	F	2		88.3	94	0.94	0.013	0.0019
Kidney	M	2		118.2	91	1.30	0.220	-0.0038
	F	2		111.1	94	1.18	0.109	-0.0017
Brain and other CNS	M	2	Yes	115.1	92	1.25	0.022	-0.0019
	F	3	Yes	91	92	0.99	0.009	-0.0006
Thyroid	M	1		92.9	95	0.98	0.980	-0.0846
	F	1		85.1	95	0.90	0.280	-0.0343
Non-Hodgkin's lymphoma	M	2		145	93	1.56	0.190	-0.0014
	F	2	Yes	134	92	1.46	0.080	-0.0008
Hodgkin's disease	M	1	Yes	111.8	95	1.18	0.040	0.0097
	F	2		120.4	93	1.29	0.190	-0.0088
Multiple myeloma	M	1	Yes	92.6	91	1.02	0.029	0.0013
	F	1	Yes	124.7	92	1.36	0.590	-0.0045
Leukaemia	M	2	Yes	134	91	1.47	0.540	-0.0036
	F	2	Yes	139.1	92	1.51	0.034	0.0000
All other malignancies ⁴	M	1		119.2	95	1.25	0.410	-0.0004
	F	1		113.1	95	1.19	0.230	-0.0039
All malignancies combined ⁵	M	-	-	-	-	-	-	-
	F	-	-	-	-	-	-	-

¹ Age by follow-up (i.e. time since diagnosis) interaction term

² Significance of the period term in the selected model

³ Variance of the true systematic effects

⁴ Including ICD9 140, 142, 146-149, 152, 155, 156, 158, 159, 160, 163, 164, 165, 170, 171, 175, 179, 181, 184, 187, 190 and 194-199

⁵ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

Table 4.5 continued.

Cancer	Sex	Relative Risk ¹		Expected excess cancer deaths ²	Avoided (crude) ³ N	Avoided (shrunk) ⁴ N %	
		Initial	Shrunk				
Oral cavity	M	0.98	1.00	429	0	0	0.0
	F	0.97	1.00	224	0	0	0.0
Oesophagus	M	0.91	0.97	1,587	111	45	2.8
	F	0.98	1.00	1,302	0	0	0.0
Stomach	M	0.90	0.92	2,349	194	193	8.2
	F	0.94	1.00	1,578	0	0	0.0
Colon	M	0.89	0.92	2,234	251	188	8.4
	F	0.88	0.90	2,571	313	256	10.0
Rectum	M	0.88	0.90	1,408	183	147	10.4
	F	0.86	0.89	1,075	155	121	11.3
Pancreas	M	0.99	1.00	1,135	0	0	0.0
	F	0.97	1.00	1,233	0	0	0.0
Larynx	M	0.97	1.00	374	0	0	0.0
	F	1.15	1.00	101	0	0	0.0
Lung	M	0.97	1.00	11,663	0	0	0.0
	F	0.99	1.00	7,013	0	0	0.0
Melanoma	M	0.83	0.88	177	35	22	12.4
	F	1.01	1.00	162	0	0	0.0
Breast	F	0.79	0.79	3,553	930	738	20.8
Cervix uteri	F	0.96	1.00	680	0	0	0.0
Body of the uterus	F	0.85	0.90	377	62	38	10.1
Ovary	F	0.89	0.92	1,695	169	136	8.0
Prostate	M	0.89	0.92	2,720	337	214	7.9
Testis	M	0.80	1.00	56	0	0	0.0
Bladder	M	0.81	0.83	1,157	256	196	16.9
	F	0.87	0.92	728	102	61	8.4
Kidney	M	0.93	1.00	748	0	0	0.0
	F	0.90	1.00	549	0	0	0.0
Brain and other CNS	M	0.88	1.00	702	0	0	0.0
	F	0.84	1.00	533	0	0	0.0
Thyroid	M	0.99	1.00	35	0	0	0.0
	F	0.83	1.00	73	0	0	0.0
Non-Hodgkin's lymphoma	M	0.93	1.00	854	0	0	0.0
	F	0.92	1.00	892	0	0	0.0
Hodgkin's disease	M	0.74	0.82	91	30	16	17.9
	F	0.81	1.00	84	0	0	0.0
Multiple myeloma	M	0.86	0.93	453	64	31	6.8
	F	1.04	1.00	499	0	0	0.0
Leukaemia	M	0.97	1.00	742	0	0	0.0
	F	0.88	0.99	610	67	8	1.3
All other malignancies ⁵	M	1.01	1.00	4,397	0	0	0.0
	F	0.96	1.00	3,748	0	0	0.0
All malignancies combined ⁶	M	-	-	33,311	1,461	1,053	3.2
	F	-	-	29,281	1,799	1,359	4.6

¹ Relative risk of excess mortality due to cancer in 1991-95 compared to 1986-90² Estimated from the model-based relative survival estimates³ Observed minus expected model-based excess mortality due to cancer (no adjustment for random variation)⁴ Observed minus expected model-based excess mortality due to cancer (adjusting for random variation)⁵ Including ICD9 140, 142, 146-149, 152, 155, 156, 158, 159, 160, 163, 164, 165, 170, 171, 175, 179, 181, 184, 187, 190 and 194-199⁶ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

The results for individual cancers were generally very different using the two methods of analysis (Table 4.6), however, the overall estimates for "all malignancies combined" were similar when the crude modelled estimates were compared to the standardisation estimates. When random variation in the data is not accounted for, the two techniques are actually computationally quite similar; the main difference being that the modelling analysis uses the modelled estimates of relative survival in its calculations rather than the observed estimates. This would imply that the model-based relative survival estimates are quite different than the observed estimates for some intervals or age groups. This may reflect instability in the original estimates, particularly at younger ages or in later follow-up intervals when there are fewer deaths.

Table 4.6: Comparison of the two methods of calculating avoided deaths due to improvements in survival: patients diagnosed in Scotland during 1991-95 compared to 1986-90

Cancer	Standardisation	Modelling (crude)	Modelling (shrunk)	Difference ¹
Oral cavity	34	0	0	34
Oesophagus	42	111	45	-3
Stomach	82	194	193	-111
Colon	537	564	445	92
Rectum	284	338	268	16
Pancreas	0	0	0	0
Larynx	10	0	0	10
Lung	86	0	0	86
Melanoma	48	35	22	26
Breast (females)	1,026	930	738	288
Cervix uteri	31	0	0	31
Body of the uterus	56	62	38	18
Ovary	28	169	136	-108
Prostate	466	337	214	252
Testis	17	0	0	17
Bladder	353	359	257	96
Kidney	68	0	0	68
Brain and other CNS	49	0	0	49
Thyroid	13	0	0	13
Non-Hodgkin's lymphoma	49	0	0	49
Hodgkin's disease	40	30	16	23
Multiple myeloma	3	64	31	-28
Leukaemia	43	67	8	35
Other malignancies ²	-49	0	0	49
All malignancies combined³	3 316	3 260	2 411	904

¹ Difference between standardisation analysis and model analysis with shrunk estimates

² Including ICD9 140, 142, 146-149, 152, 155, 156, 158, 159, 160, 163, 164, 165, 170, 171, 175, 179, 181, 184, 187, 190 and 194-199

³ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

After accounting for random variation, the model estimates of avoided deaths were substantially reduced and the estimated number of avoided of deaths for "all malignancies combined" was 2 411 (compared to 3 316 with the standardisation method). The proportion of avoided deaths was similar (3.9% for shrunken model estimates compared to 4.6% for standardisation estimates) because the expected number of excess cancer deaths varied between the two methods.

Avoidable deaths (comparing deprivation groups within Scotland)

A deprivation gradient in survival has been observed for most cancers in Scotland (see *Chapter 3*), and estimates have been made using the standardisation method, of the number of deaths that could be avoidable if patients in lower deprivation groups had the same survival as those in the most affluent group.

The most affluent group had, by definition, zero avoidable deaths and the numbers of avoidable deaths in the other deprivation groups compared to the affluent group were calculated separately and then summed. When the data was stratified by age, sex and deprivation category there were some strata with too few cases to perform an analysis (Table 4.7) and so age-truncated analyses were performed. For patients with thyroid cancer and Hodgkin's disease there were a number of strata with too few cases and so these cancers were excluded from the analysis altogether.

Overall, 2 490 (2.6%) excess cancer deaths could have been avoidable within five years of diagnosis for patients diagnosed in Scotland in 1991-95 if all deprivation groups had the same survival as the most affluent group. The largest numbers of avoidable deaths were seen for patients with cancers of the breast (589 deaths avoidable), large bowel (492) and bladder (248). The cancers for which there were the largest deprivation-specific variations in survival were malignant melanoma of the skin (20% of deaths would be avoidable), testicular (19%), cervix uteri (18%), breast (15%), bladder (12%) and kidney (10%).

Table 4.7: Avoidable deaths within five years of diagnosis if all deprivation groups had the same survival as the most affluent group using the standardisation method: patients diagnosed in Scotland during 1991-95

Cancer	Number of cases	Age range included by sex	Cases included	Number of excess cancer deaths ¹		Avoidable	
				% Observed	Expected	N	%
Oral cavity	1,261	F 45-74, M 15-74	92.1	681	665	-19	-2.8
Head and neck	3,874	F 45-99, M 15-99	98.6	2,195	2,001	43	2.2
Oesophagus	3,293	45-99	98.3	3,017	3,023	16	0.5
Stomach	4,722	F 45-99, M 15-99	99.1	4,219	4,195	190	4.5
Large bowel	14,420	15-99	100.0	9,152	8,087	492	6.1
Colon	9,614	15-99	100.0	6,068	5,347	280	5.2
Rectum	4,806	15-99	100.0	3,084	2,779	203	7.3
Pancreas	2,541	F 55-99, M 45-99	95.4	2,365	2,373	6	0.2
Larynx	1,308	F -, M 45-84	84.2	528	457	2	0.5
Lung	20,850	15-99	100.0	19,670	19,687	98	0.5
Melanoma	2,545	F 15-99, M 15-84	98.7	575	435	85	19.5
Breast (females)	14,448	15-99	100.0	4,875	4,026	589	14.6
Cervix uteri	1,859	15-84	97.5	707	693	121	17.5
Body of the uterus	1,518	15-84	94.3	445	372	21	5.6
Ovary	2,507	15-99	100.0	1,826	1,830	0	0.0
Prostate	7,151	45-99	99.9	4,276	3,320	120	3.6
Testis	843	15-54	93.2	45	43	8	18.8
Bladder	6,063	F 45-99, M 15-99	99.3	2,898	2,148	248	11.5
Kidney	2,250	15-99	100.0	1,500	1,437	138	9.6
Brain and other CNS	1,515	15-84	98.8	1,248	1,256	18	1.4
Thyroid	508	F 15-54, M 85-99	44.1				
Non-Hodgkin's lymphoma	3,323	15-99	100.0	2,028	1,952	97	5.0
Hodgkin's disease	631	15-54	56.6				
Multiple myeloma	1,338	F 55-99, M 55-84	88.9	995	985	11	1.1
Leukaemia	2,136	15-99	100.0	1,556	1,525	15	1.0
Other malignancies ²	10,707	15-99	100.0	9,428	9,522	149	1.6
All malignancies³	109,042		98.8	73,074	68,966	2,490	3.6

¹ Excess deaths = number of cases x (1 - relative survival rate)

² Including ICD9 152, 155-156, 158-159, 163-165, 170-171, 175, 179, 181, 184, 187, 190 and 194-199

³ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

Avoidable deaths (comparing Scotland to Europe)

The number of cancer deaths that could be avoidable within five years of diagnosis among cancer patients diagnosed in Scotland during 1985-89 if survival rates for these patients was (i) equivalent to the weighted European average, and (ii) equivalent to the European best, have next been considered (Table 4.8). The "best" survival was calculated as the *analysis weighted* average of the cancer-, sex- and age-specific relative survival estimates of the three countries with highest age-standardised relative survival. The standardisation method was used because there was not enough information available on the Eurocare CD Rom to implement the modelling method.

Table 4.8: Avoidable deaths within five years of diagnosis if survival in Scotland was the same as (i) the European weighted average and (ii) the European best, using the standardisation method: patients diagnosed 1985-89

Cancer	Cancer cases		Expected excess cancer deaths ¹	Avoidable (European average)		Avoidable (European Best)	
	N	% included		N	%	N	%
Oral cavity	707	93.2	376	-17	-4.6	118	31.3
Head and neck ²	3,201	93.0	1,431	-55	-3.8	338	23.6
Oesophagus	2,872	92.3	2,677	52	2.0	85	3.2
Stomach	6,165	90.8	5,524	704	12.7	935	16.9
Large bowel	14,418	92.0	8,701	909	10.4	1,975	22.7
Colon	9,678	91.5	5,723	642	11.2	1,316	23.0
Rectum	4,740	92.9	2,979	267	9.0	658	22.1
Pancreas	3,081	90.1	2,979	19	0.7	75	2.5
Larynx	1,215	93.2	456	-7	-1.5	148	32.5
Lung	23,326	89.9	21,976	888	4.0	1,899	8.6
Melanoma	2,280	94.4	404	-147	-36.5	35	8.7
Breast (females)	13,400	91.9	4,758	1,176	24.7	1,956	41.1
Cervix uteri	2,189	95.6	885	58	6.5	238	26.9
Body of the uterus	1,663	93.1	503	56	11.1	206	41.0
Ovary	2,698	91.5	1,944	108	5.6	364	18.7
Prostate	5,986	91.5	3,189	675	21.2	1,134	35.6
Testis	708	97.7	58	-15	-26.0	4	7.6
Bladder	6,097	93.7	2,423	197	8.2	636	26.2
Kidney	2,209	90.6	1,443	307	21.3	415	28.7
Brain and other CNS	1,333	95.3	1,184	80	6.8	109	9.2
Thyroid	509	92.9	161	25	15.6	90	55.7
Non-Hodgkin's lymphoma	635	98.4	228	38	16.6	60	26.4
Hodgkin's disease	3,099	93.6	1,842	167	9.1	390	21.2
Multiple myeloma	1,302	91.6	1,060	127	12.0	217	20.4
Leukaemia	2,366	87.7	1,757	217	12.4	447	25.5
Other malignancies ³	3,439	88.2	2,589	41	1.6	163	6.3
All malignancies⁴	102,976	91.5	67,717	5,630	8.3	11,771	17.4

¹ Excess deaths = number of cases x (1- relative survival rate)

² Calculated as the sum of estimates for ICD9 140, 141, 142, 143-5, 146, 147, 148, 160 and 161

³ Calculated as the sum of estimates for ICD9 152, 155, 156, 163, 170, 171, 187 and 190

⁴ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

European average: for most cancers the European average survival was higher than that in Scotland, the exceptions being oral cavity, head and neck, laryngeal and testicular cancers, and malignant melanoma of the skin. The largest numbers of avoidable deaths, over the period 1985-89, arose for breast (1 176, 25% of excess deaths from this cancer), prostate (675, 21%) and kidney (307, 21%) cancer. Over 10% of deaths were also potentially avoidable for cancers of the stomach, colon, corpus uteri and thyroid, and for multiple myeloma, non-Hodgkin's lymphoma and leukaemia. Overall, 5 630 deaths were avoidable for patients diagnosed during 1985-89, equating to over 1 000 (8%) cancer deaths per annum.

European best: for all cancers the European best was higher than that in Scotland. The largest number of avoidable deaths, over the period 1985-89, arose for breast (1 956, 41%), lung (1 899, 9%), colon (1 316, 23%) and prostate (1 134, 36%). More than 20% of deaths were also potentially avoidable for cancers of the oral cavity, head and neck, rectum, larynx, cervix and corpus uteri, bladder, kidney and thyroid, and all the haematological malignancies. Overall, 11 771 deaths were avoidable for patients diagnosed during 1985-89, equating to over 2 300 (17%) cancer deaths per annum. Some of these differences may be partly due to differences in the definition of the disease and the approaches commonly used for diagnosis¹⁰⁴.

Table 4.9: Avoidable deaths within five years of diagnosis if survival in Scotland was the same as (i) the European weighted average and (ii) the European best: patients diagnosed 1985-89, all malignancies combined¹, by age group

Analysis	15-44		45-54		55-64		65-74		75-99	
	N	%	N	%	N	%	N	%	N	%
European average	123	5	419	8	1,195	8	1,767	8	2,127	9
European best	608	24	1,019	20	2,190	15	3,312	15	4,705	20

¹ Calculated as the sum of the estimates from the individual cancers (excluding non-melanoma skin cancer)

The largest numbers of avoidable deaths were seen in the oldest age group (Table 4.9). In the European average analysis, the oldest age group also had the highest percentage of avoidable deaths (9%), whereas in the European "best" analysis it was the youngest age group with the largest percentage (24%) of avoidable deaths. The youngest age group was based on the smallest numbers of cases within age and sex groups and so there may be instability in some of the estimates. The difference between the European average and "best" estimates illustrate the range of improvement that could be achievable in Scotland, with between 9-20% of cancer deaths avoidable in the oldest age group if survival in Scotland improved in line with other European countries.

Discussion

There are three ways of reducing cancer mortality, namely, primary prevention (changing risk factors to reduce incidence and therefore mortality), secondary prevention (screening and earlier detection), and advancements in therapy. In Scotland, mortality from lung

cancer is decreasing in men due to a reduction in smoking prevalence, and mortality from gastric cancer is decreasing, probably due to changing diet and eradication of the *helicobacter pylori* virus. The breast screening programme which aims to detect cancer at an earlier stage has been running for 13 years and the cervical screening programme which aims to detect cancers before they become malignant has also been running for 13 years on an organised, national basis. All of these factors should lead to a reduction in mortality without advances in therapy.

As well as the national screening programmes in Scotland, earlier detection may also be beneficial for colorectal and prostate cancers, and malignant melanoma of the skin. A pilot of colorectal screening is currently underway in Scotland (but will not influence the data analysed here), and PSA testing has become common on an ad hoc basis since the early 1990s to detect prostate cancers early. There was a major public health education programme for malignant melanoma of the skin in the 1980s, which may be responsible for earlier diagnosis of these cancers.

Some of the factors mentioned above are taken into account in the analyses in this chapter which relate specifically to changes in survival from cancer (i.e. reductions in mortality due to earlier diagnosis and improvements in treatment), but not those influencing mortality through incidence (primary prevention and cervical screening).

Overall, the avoided deaths analysis showed the reduction in the number of deaths achieved due to improvements in survival over time, with between 2 411 (3.9%) and 3 316 (4.6%) excess cancer deaths avoided for patients diagnosed during 1991-95 compared to 1986-90. Overall, 80% of the avoided deaths (using either analytic method) were due to improvements in survival for patients with cancers of the breast, large bowel, prostate and bladder.

Breast, large bowel and prostate cancers are among those for which earlier detection is beneficial, as mentioned above. Breast screening and PSA testing for prostate cancer were both introduced during the time period examined (1986-95), and this leads to potential problems in interpretation of survival data due to lead-time and length bias. These issues are discussed in detail in Chapter 5. There have been substantial advances in the treatment of breast cancer over the time period, so at least some of the improvement observed is likely to

be real. There is also a possible problem of bias in the survival estimates for bladder cancer, due to a change in the definition for coding. A large proportion of bladder tumours are papillomas, which have very good prognosis and can be difficult to diagnose unequivocally as invasive, and over time there may have been an increasing tendency for such papillomas to be registered with the malignant code (see Chapter 7).

Putting these potential data problems to one side, the proportion of deaths avoided increased for patients diagnosed over the whole 25 year time period studied (1971-95). For patients diagnosed during 1986-90, 3.7% of deaths were avoided within 5 years of diagnosis and 2.9% of deaths within 10 years of diagnosis (Table 4.4). This provides evidence that an increasing number of patients are being cured of cancer, particularly as noted previously, for patients with testicular and thyroid cancer, and leukaemia. This is most likely a reflection of major advancements in therapy for these cancers.

The second analyses investigated the additional numbers of deaths that could be avoidable in Scotland if survival variations between deprivation groups were removed. It is important to also consider that the prevalence of many risk factors that have been linked to cancer (e.g. smoking, high fat diet, alcohol consumption) also vary between deprivation groups; often to the detriment of the more deprived groups. Therefore, if deprivation-specific survival variations were removed, there may still be differences in mortality from cancer by deprivation group, because of a higher incidence of cancer in these patients.

Overall, 2 490 (3.6%) cancer deaths could be avoidable within 5 years of diagnosis, if patients in all deprivation groups achieved the survival of those in the most affluent group. The largest numbers of avoidable deaths were for patients with breast, large bowel, bladder and lung cancer; jointly accounting for around two-thirds of the avoidable deaths. Important differences in survival were also identified for patients with melanoma of the skin, and cancers of the testis, cervix and kidney. Chapters 5 - 8 of this thesis look in detail at why there are variations in cancer survival between deprivation groups in Scotland. The cancers investigated in-depth are those with the largest number of avoidable deaths of patients diagnosed during 1991-95, namely, breast, large bowel and bladder cancers, and those with the largest proportions of avoidable deaths, namely, malignant melanoma of the skin and kidney cancer. Other cancers with a large number or percentage of avoidable deaths were prostate cancer, which was not considered due to the potential confounding of

PSA testing; cervical and testicular cancers, which were not considered due to the small number of cases involved; and lung cancer, which was not considered because the difference in survival between deprivation groups was actually small, but is significant because of the large number of patients involved.

The third analyses investigated the numbers of deaths that could be avoidable in Scotland if survival was the same as in other European countries. It is argued that European countries that are only represented by a small proportion of the countries population in EURO CARE should not be included in such comparisons, as the selected area may not be representative of the country (e.g. for Austria and Sweden). However, even the survival estimates for the most affluent patients in Scotland do not achieve the survival observed for these "non-representative" countries for many cancers (data not shown).

We could restrict the analysis to only those countries with complete coverage (Denmark, Estonia, Finland, Iceland, Slovakia and Slovenia) but this would equally not be representative of Europe as a whole. It has been suggested that survival in Great Britain should be compared to that in the Nordic countries (included Denmark, Finland, Sweden and Iceland), as these countries are known to have very good cancer registration data¹²³ and have similar life styles to the UK. If we had used the average survival of only these countries in the analyses shown in Table 4.9, then 4 039 (6%) cancer deaths could have been avoidable per annum (data not shown) compared to the estimate of 5 630 (8%) when all the European data was used for the analyses. Although the number of avoidable is reduced somewhat, it still represents a substantial number of avoidable deaths.

The relative survival estimates for 1985-89, available on the EURO CARE II CDROM, are not recorded with decimal places. This may have introduced bias in the computation of avoided deaths, although the direction of the bias will vary between cancers. It is possible that some of the differences in survival between countries in Europe may be due to variations in disease definitions and in the approaches commonly used for diagnosis^{104,124}. For breast cancer, which had the largest number of avoidable deaths, the survival estimates are complicated by screening, which was introduced across Europe over a large time window and was not introduced in Scotland until near the end of the period of analysis. However, the proportion of avoidable deaths was not higher for women in the screening age groups: the biggest proportion of avoidable deaths was for women aged 75 and over, for

whom 35% of deaths were estimated to be avoidable compared to the European average. For all cancers combined, the number of avoidable deaths increased with increasing age and so did the percentage of avoidable deaths. This poses questions about the treatment of older patients in Scotland.

The results of the European "best" analyses were highly dependent on the weightings used. If the three countries with the highest age-standardised relative survival rates were used to define "best", the resulting estimates are much lower than if the countries with the highest age- and sex-specific relative survival rates were used (data not shown). The "best" countries were defined as those with the highest age-standardised relative survival estimates in this Chapter, because they are more stable. The age- and sex-specific relative survival estimates for the three "best" countries could be combined giving them equal weight or by weighting them according to the proportion of cases they contribute to the analysis. Choice of analysis weights or equal weights did not greatly affect the estimates of avoidable deaths (data not shown).

There are limitations that effect both of the analytical methods used in this chapter. Firstly, the calculation of avoided deaths covers a finite follow-up interval, five years, and so does not represent the number of deaths avoided due to changes in the effective "cure" of patients over time. Secondly, there are problems because some estimates are based on few cases. The model-based estimates, which are essentially smoothed, will tend to give more conservative estimates of avoided deaths when the analyses are based on small numbers of cases or deaths.

The comparison of the two analytic methods is complicated because the survival estimates being used for the analyses may vary because of the different methods of calculating relative survival used. Additionally, the results from the STATA algorithm are sensitive to the number of break options selected, particularly for rare or very fatal cancers (see Chapter 1). Partly because of these two factors, the proportion of avoided deaths estimated by the two methods is more similar than the absolute number of avoided deaths. Additionally, the contribution of the cancers with the largest proportions of avoided deaths are very similar, when again, the absolute numbers differ. When the analyses are not based on very large samples of patients, as in this chapter, it may be more appropriate to present avoided deaths in terms of proportion of excess cancer deaths avoided rather than in absolute numbers.

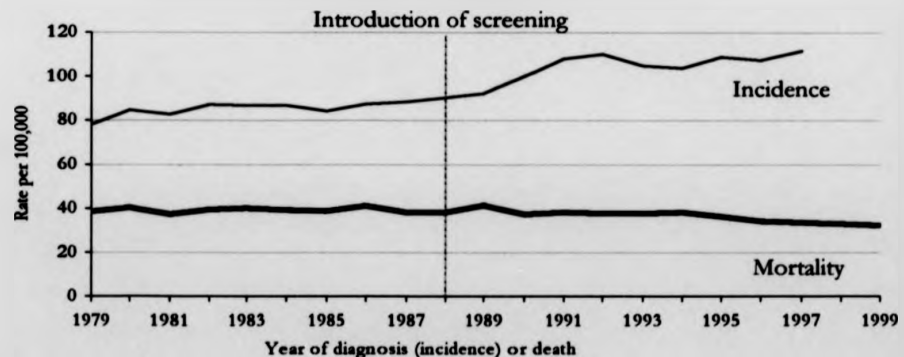
In conclusion, calculation of avoided and avoidable deaths is a novel and interesting approach to looking at improvements in cancer survival. Two methods to compute these statistics were introduced. Overall, between around 500 and 650 deaths have been avoided per year in Scotland for patients diagnosed during 1991-95 due to improvements in survival from 1986-90. Additionally, if differences in survival between deprivation groups in Scotland could be removed, up to 500 deaths a year could be avoidable.

BREAST CANCER

Background

Breast cancer is the most common cancer among women in Scotland, accounting for 25% of all cancers, with a total of 3 374 new cases of invasive disease diagnosed in 1997. Incidence has been increasing over time since the 1970s, and has increased at an even greater rate in the 1990s, partly due to the introduction of the Scottish National Breast Screening Programme (SNBSP). Mortality from breast cancer had also been increasing until the late 1980s, since when there has been a 28% reduction (Figure 5.1). A similar reduction has also been observed in England^{125,126} and the United States¹²⁷. In 1999, 1 129 women died of breast cancer in Scotland.

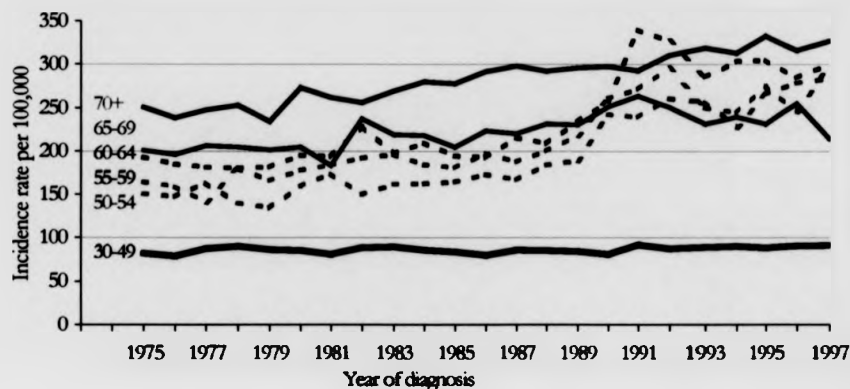
Figure 5.1: Breast cancer in Scotland: trends in incidence (1979-1997) and mortality (1979-1999), all ages (European age-standardised rates)



As for many cancers, age is the most important known influence on incidence (Figure 5.2), with the highest risk in the elderly. Risk in women of screening age (50-64 years) has increased faster than expected from the underlying trend, whereas incidence in women aged

65-69 years appears to have levelled off in the 1990s. Risk varies markedly between countries (Figure 5.3) with slightly higher rates in Scotland than in England and Wales.

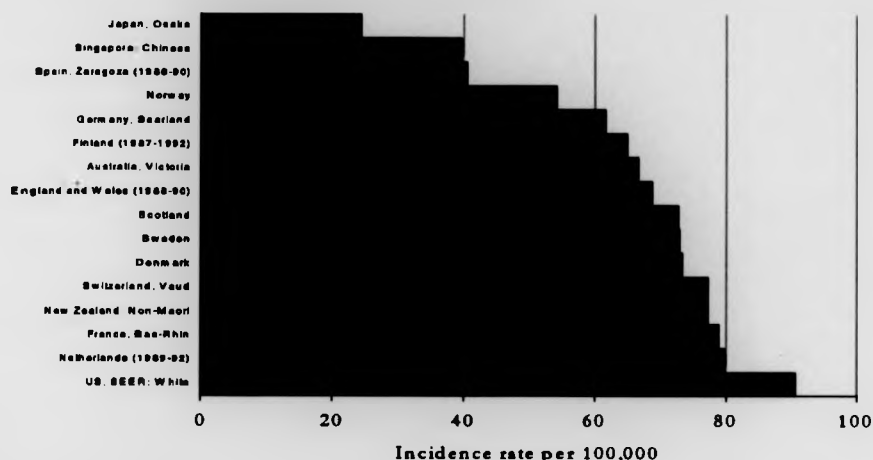
Figure 5.2: Breast cancer in Scotland: trends in incidence (1975-1997), by age band



The SNBSP was introduced in 1988 for women aged 50-64 and the first (prevalent) round completed in 1994. The first time that women are screened (prevalent round), breast screening picks up many small and slow-growing tumours, some of which might not have presented clinically until later, if at all. The detection at screening of a large number of cancers with relatively good prognosis, which might never present symptomatically in a woman's life-time, is known as length bias¹²⁸. It may explain why incidence is still higher than would be expected from a projection of the underlying historical trends. Length bias would affect both incidence and survival.

In the trial setting a reduction in mortality due to screening was seen seven years after the introduction of screening¹²⁹, however, compliance to attend screening is lower in the routine setting so a longer interval may be expected before a reduction in mortality is seen. Therefore, screening has probably played a relatively small part in the large (16%) mortality reduction observed since 1990 in Scotland. Around 30% of the corresponding reduction in England has been attributed to the direct effects of screening, with the remainder due to improved adjuvant treatments and earlier presentation outside the screening programme¹¹⁴. Other researchers believe the screening effect may be lower¹³⁰.

Figure 5.3: International comparison of breast cancer incidence, around 1988-1992 (world age-standardised rates per 100,000)



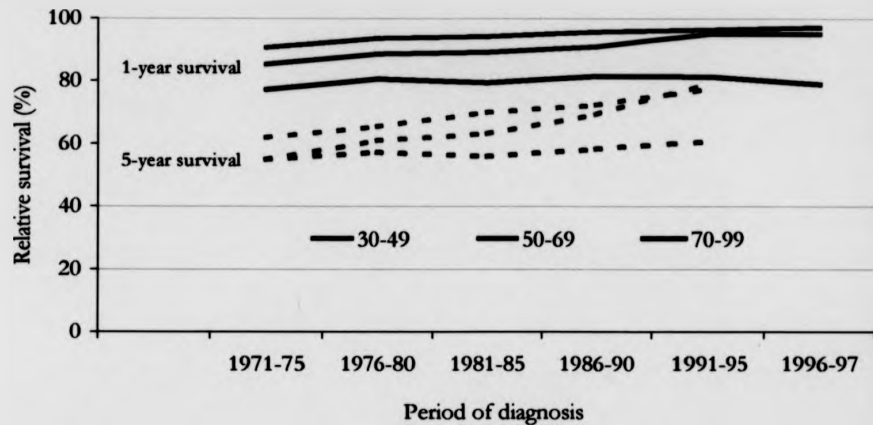
Source: Cancer Incidence in Five Continents, Volume VII¹⁰

A by-product of the screening programme has been raised diagnostic standards and improved organisation of services across all age groups, which would also be expected to have had an impact on mortality rates.

Even before the introduction of screening, breast cancer survival in Scotland was improving steadily over time, due to improvements in stage at diagnosis, and to the increasing use of radiotherapy and chemotherapy^{22,131}. For women diagnosed in 1971, the five-year relative survival rate was 53%, and for women diagnosed in 1993 this had increased to 73%. However, survival has been increasing more quickly in the age group which encompasses those invited for screening (ages 50-69; Figure 5.4).

The introduction of the screening programme complicates interpretation of the survival trends in the age range 50-69 because of length bias (very slow growing tumours) and lead-time bias (where the time of diagnosis is advanced but death is not delayed). The prevalent round of screening was completed in Scotland by the end of 1994, and survival might be expected to improve for women diagnosed during this round. However, it is sustained for women diagnosed after 1994, when most women had incident (second and subsequent) screens and is more pronounced at five years after diagnosis than at one year after diagnosis.

Figure 5.4: Women diagnosed with breast cancer in Scotland during 1971-1995: trends in relative survival by age band



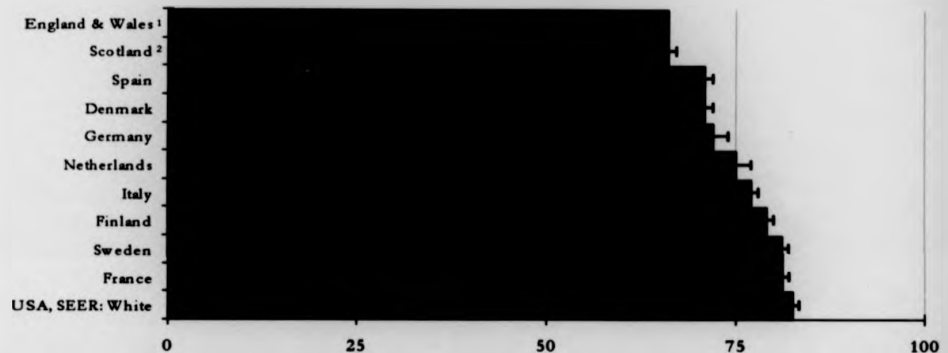
This is not typical of lead-time bias. The sustained improvement in survival could be due to the enhanced effectiveness of treatment being given at an earlier stage, in other words, the desired effect of screening, or it could be caused by length bias.

Length bias could play a role because incidence of breast cancer is higher in more affluent women, and compliance with screening was initially higher in these women, who also have better than average underlying mortality rates. If a large number of affluent women were diagnosed with tumours that would not have presented clinically for a long time, then we would see survival increasing with time since diagnosis. The data analysed in detail in this chapter relate to 1997, 10 years after the introduction of screening, so the effects of lead time and length bias should be small.

Survival from breast cancer in Scotland is lower than in other countries in Europe⁶ and the USA (Figure 5.5). Several factors have been linked to poor breast cancer survival. These include co-morbidity¹³²; tumour type, with invasive lobular carcinoma conferring better prognosis than invasive ductal carcinoma¹³³; patient delay but not GP delay¹³⁴; long-term oral contraceptive use¹³⁵; treatment by a non-specialist surgeon²⁷; low clinician workload²⁶, and differences in the use of systemic adjuvant therapy¹³⁶. One study found survival was poorer during the holiday months of the year when medical teams may be under-represented¹³⁷. A study in Yorkshire found that hospitals with a special interest in breast cancer used more up-

to-date methods and made more treatment options available¹³⁸. In East Anglia, being treated at a specialist hospital was significantly beneficial in women aged under 75 years at diagnosis³¹, even after accounting for tumour stage. There is strong evidence that women managed by a multidisciplinary team do better^{22,26,27}.

Figure 5.5: Breast cancer: international comparison of five-year relative survival (with 95% confidence intervals), selected countries, women diagnosed around 1985-1989, all ages



¹ Women diagnosed 1986-90, aged 15-99

² Women aged 15-99

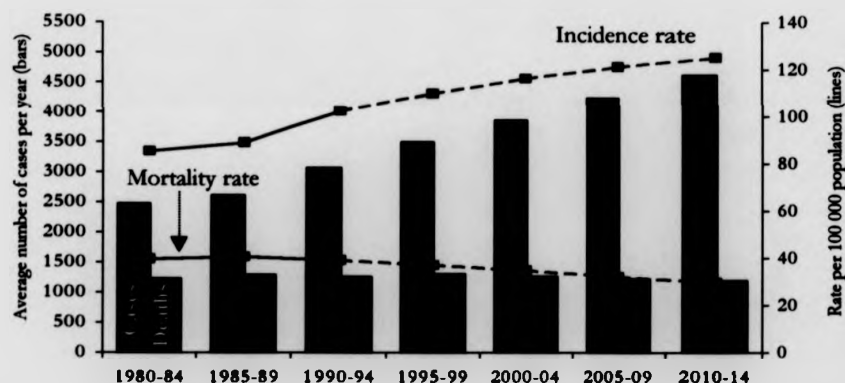
Sources: Berrino *et al.*⁶, Gatta *et al.*¹³⁹, Coleman *et al.*⁴

Breast cancer is more common among affluent women, but survival is also better in these women^{4,13,16,140}. Geographic and socio-economic differences in investigation and treatment have been reported in the UK and Europe^{18,19,141,142}. There is conflicting evidence on whether these differences remain after adjustment for stage at diagnosis, with differences remaining for studies in south-east England^{13,16}, Finland³⁴ and Glasgow¹⁵ and conflicting evidence from a different Glasgow study¹⁴³, and studies from The Netherlands¹⁴⁴ and Australia¹⁴⁵. Tumour stage is a very significant prognostic indicator for breast cancer survival^{13,16,144,146} and is linked to delay at diagnosis¹⁴⁷, however, within each category of tumour stage, delay was not found to be an important prognostic factor in an Argentinean study¹⁴⁸. In south-east England it was found that the low social classes were more likely to present as an emergency admission and less likely to have surgical interventions¹⁴⁹. Tumour morphology does not appear to account for social class differences in Scotland¹⁵. Oestrogen receptor negative tumours have been linked both to poor survival and to social class¹⁵⁰, but

in an audit of Scottish women diagnosed in 1987, only a third of the effect of deprivation on survival could be accounted for by differences in oestrogen receptor status^{22,151}.

Projections of recent trends in incidence and mortality in Scotland¹⁵² suggest a further large increase in breast cancer incidence in the decade up to 2010, and a continuing decline in mortality rates (Figure 5.6). There could be as many as 4 775 cases diagnosed per year in 2010. These trends underline the public health importance of breast cancer and the continuing need to understand and further improve survival from breast cancer.

Figure 5.6: Projections of breast cancer incidence and mortality in Scotland (numbers of cases and deaths, and European age-standardised rates)



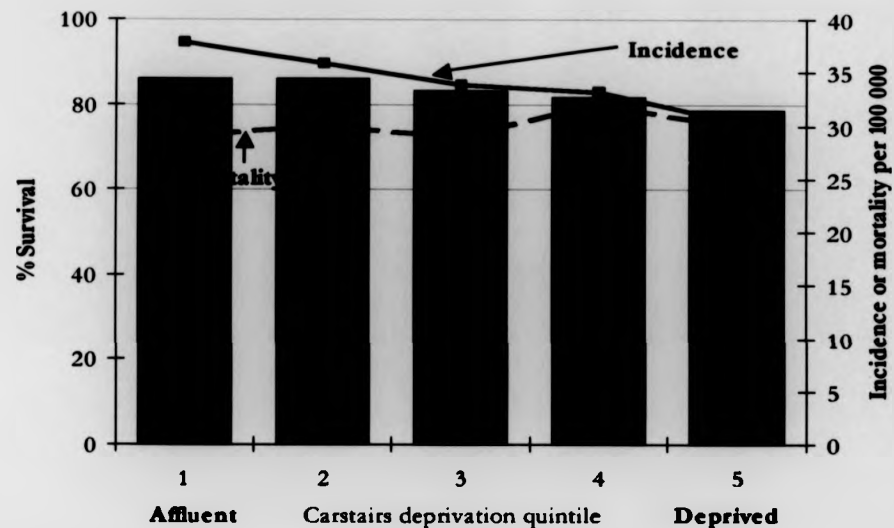
In this chapter, the survival of 3 309 women diagnosed with breast cancer in Scotland in 1997 is investigated to identify reasons for differences in survival by deprivation category. For definitions of the variables included in the analyses, please refer to Chapter 2.

Results and commentary

For women diagnosed in Scotland in 1997, incidence was 25% higher in women from the most affluent areas (37.8 per 100 000; herein referred to as the affluent group or affluent women) compared to women from the most deprived areas (30.3; the deprived group or deprived women). The mortality rates (for women dying in 1999) show very little variation across deprivation groups. The deprivation-specific trend in incidence is not matched by a

similar trend in mortality because of differentials in survival, with two-year survival 8% higher in the affluent (85.3%) than the deprived (77.5%) group (Figure 5.7).

Figure 5.7: Women diagnosed with breast cancer in Scotland in 1997: incidence¹ and two-year relative survival², and mortality¹ in 1999, by deprivation category



¹ Age-standardised rates per 100 000 person-years at risk (European standard population)

² Using deprivation-specific life tables; age-standardised using the world standard cancer patient population

Of the 3 309 women diagnosed with breast cancer in 1997, 1 418 (43%) were from deprivation groups 1 and 2 and 1 240 (37%) from deprivation groups 4 and 5 (Table 5.1). The median age of diagnosis was 61 years with inter-quartile range from 51 to 74 years, with no significant difference in age at presentation between the deprivation groups. Breast cancer was the first primary malignancy for 3 104 (94%) women, with 3% having had a previous breast cancer and a further 3%, a previous primary at another site. These proportions were similar between the deprivation groups, so the fact of a previous primary was not included in the multivariate analyses.

Deprived women mainly came from urban areas (81% compared to 41% for affluent women). Almost 80% of the most deprived women were resident in only three of the fifteen health boards: Greater Glasgow Health Board (GGHB; 50%), Lanarkshire (17%) and

Argyll and Clyde (12%). Within health board the mix of deprivation categories amongst women with breast cancer varied very widely (for example, GGHB: 50% deprived and 19% affluent; Lothian and Borders: 7% deprived and 28% affluent; Grampian: 3% deprived and 54% affluent).

Table 5.1: Women diagnosed with breast cancer in Scotland in 1997: demographic data by deprivation category (number and percentage of cases)

Deprivation category	Number (%) of cases	Median age (inter-quartile range)	Cases for which:			Urban resident ¹
			First primary	Previous breast primary	Previous primary elsewhere	
Affluent	734 (22%)	61 (51-73)	697 (95%)	20 (3%)	17 (2%)	302 (41%)
2	684 (21%)	60 (51-73)	642 (94%)	19 (3%)	23 (3%)	153 (22%)
3	651 (20%)	61 (51-73)	615 (94%)	20 (3%)	16 (2%)	161 (25%)
4	644 (19%)	62 (51-74)	593 (92%)	22 (3%)	29 (5%)	291 (45%)
Deprived	596 (18%)	63 (53-75)	557 (93%)	19 (3%)	20 (3%)	485 (81%)
Total	3,309 (100%)	61 (51-74)	3,104 (94%)	100 (3%)	105 (3%)	1,392 (42%)

¹ Chi-square test for association between urban residence and deprivation: $p < 0.001$

Organisation of services

The Calman-Hine report¹⁰¹, published in 1995, recommended that specialist cancer teams in locations with the necessary specialist resources should manage women with breast cancer in England and Wales. The Scottish Cancer Coordinating and Advisory Committee (SCCAC) proposed a similar network for Scotland in 1996¹⁰², with the aim that all women should have access to high levels of specialist cancer care to provide optimal treatment. Audit data for women diagnosed in 1987 and 1993 showed that older women and those living in more deprived areas were less likely to travel to a cancer centre¹⁵³. These disparities, whether appropriate or not, are still present. Among women diagnosed in 1997, 81% of those aged under 75 attended one of the regional centres with radiotherapy provision (regional RT centre) within their cancer spell, but only 50% of those aged over 75. Of the affluent women, 81% attended a regional RT centre compared to 64% of deprived women (Table 5.2). It is, therefore, evident that inequalities in access to treatment by age and deprivation were still prevalent in 1997.

Overall, 74% of women attended a regional RT centre at some point during their cancer spell (Table 5.2), a further 10% attended other high-workload hospitals, 9% medium-

workload hospitals and 6% low-workload hospitals (data not shown). The main hospital of treatment was a regional RT centre for 58% of affluent women and 35% of deprived women. A correspondingly higher proportion of deprived women were treated at other high-workload hospitals (9% affluent and 34% deprived). These gradients were seen for women living in both urban and rural areas; however, deprived urban residents were less likely to attend a regional RT centre or other high-workload hospital (74% compared to 85% of affluent urban women).

There were also differences in the proportion of women seen by a high-workload consultant (seeing at least 30 breast cancer cases per year), with those from the affluent areas more likely to see a high-workload consultant (66% compared to 56% in the deprived group). Those from the deprived areas were seen by more medium-workload consultants (10-29 cases; 19% compared to 12% for affluent women), with similar proportions being seen by only a low-workload consultant (12% compared to 10% for affluent women). The proportion of women for whom no details of contact with a consultant physician were recorded (around 11%), was similar between the deprivation groups.

The majority (87%) of women were seen in a specialist department (85% within 3 months of diagnosis), but with less likelihood for deprived women (81%). Women from the deprived group were more likely to have been initially admitted as an emergency (13% compared to 9% of affluent women; $p=0.016$).

Delay

For over half (51%) of the 3 233 women with a known treatment date, at least two weeks elapsed between diagnosis and definitive treatment (Table 5.2). Women from deprived areas were less likely to have a wait (45% waited at least 2 weeks compared to 50% of affluent patients; $p<0.001$). Over half (58%) of women were seen throughout their cancer spell at one hospital, with 38% of women were seen at two hospitals. Deprived women were more likely to stay in hospital between diagnosis and treatment (86% compared to 69% of affluent women). These factors could reflect poorer health of these women at admission, or varying hospital policy, or lack of support to return home.

Table 5.2: Women diagnosed with breast cancer in Scotland in 1997: access to health care by deprivation category (number and percentage of patients)

Deprivation category	No. of cases	Attended a regional RT centre ¹	Attended a specialist department ²	Main treatment at a regional RT centre	Treated in a high-workload hospital ³	Seen by a high-workload consultant ⁴	Emergency admission	Treated at first admission	More than two weeks' delay between diagnosis and treatment ⁵	All of care in one hospital
Affluent	734	592 (81%)	623 (85%)	424 (58%)	491 (67%)	484 (66%)	63 (9%)	506 (69%)	358 (50%)	445 (61%)
2	684	526 (77%)	604 (88%)	312 (46%)	418 (61%)	451 (66%)	51 (7%)	529 (77%)	386 (57%)	391 (57%)
3	651	475 (73%)	558 (86%)	257 (39%)	408 (63%)	395 (61%)	60 (9%)	493 (76%)	346 (54%)	359 (55%)
4	644	463 (72%)	553 (86%)	238 (37%)	417 (65%)	386 (60%)	69 (11%)	494 (77%)	308 (49%)	345 (54%)
Deprived	596	379 (64%)	481 (81%)	206 (35%)	413 (69%)	332 (56%)	77 (13%)	512 (86%)	262 (45%)	378 (63%)
Total	3,309	2,435 (74%)	2,819 (85%)	1,437 (43%)	2,147 (65%)	2,048 (62%)	320 (10%)	2,534 (77%)	1,660 (51%)	1,918 (58%)
Significance ⁶		$p<0.001$	$p=0.038$	$p<0.001$	$p=0.012$	$p<0.001$	$p=0.016$	$p<0.001$	$p<0.001$	$p=0.002$

¹ At some point in the cancer spell

² Within 3 months of diagnosis

³ Hospital seeing at least 104 breast cancer patients per year (see Chapter 2 for details of the workload groupings)

⁴ Consultant who saw at least 30 breast cancer patients in 1997 (see Chapter 2 for details of the workload groupings)

⁵ Days between diagnosis and definitive treatment; percentage of 3 233 patients with a definitive treatment date

⁶ Chi-square test for association

Mode of presentation

When a woman presents with a suspected breast tumour, a clinical assessment is usually performed, followed by a fine needle aspiration, biopsy and possibly a mammogram, to confirm diagnosis. Once malignancy is confirmed, a pathological (surgical) examination is then performed to establish the size and nodal status of the disease. Metastases are usually assessed by clinical examination or imaging. Large tumour size, nodal involvement and metastases are all important prognostic indicators associated with poor survival^{137,154,155}.

Pathological tumour size (pT) and nodal status (pN) are the most reliable prognostic indicators¹⁵⁶, and these, along with clinical stage (cTNM) have been collected on the SOCRATES database for breast tumours for patients diagnosed from 1997 onwards. Among women diagnosed in Scotland in 1997, 27% of women had no pT recorded, 23% had no pN, 15% had no cT, 19% had no cN, and 34% had no metastatic status recorded. This could be because the CRO missed the information when extracting from the medical notes, but is more often because the information is not explicitly stated in the notes. Information was more often missing in deprived women for each of these factors ($p < 0.05$). Of women with known details, there were no differences in tumour size or nodal status between the deprivation groups; however, deprived women did appear to be more likely to present with metastatic tumours ($p < 0.01$; Table 5.3).

Based on previous, more complete stage information from Scottish audits¹⁵³, 8.3% of women diagnosed in 1987 and 7.0% of women diagnosed in 1993 had metastatic disease, so it is likely that the unknowns in the 1997 data analysed here largely comprise non-metastatic cases. This is further supported by examination of the 1-year survival estimates (96% for women with non-metastatic disease, 58% for women with metastases and 86% for women whose metastatic status was unknown).

Other important prognostic indicators include tumour grade^{37,154,157} with survival decreasing as grade increases; oestrogen receptor (ER) status, with ER-negative tumours having the poorer prognosis^{155,158} and comorbidity^{141,159,162}. Among all women diagnosed in Scotland in 1997, 22% had ER-negative tumours, 59% ER-positive tumours and 20% had unknown ER status (Table 5.4; different percentages shown, see table footnote 1).

Table 5.3: Women diagnosed with breast cancer in Scotland in 1997: tumour stage by deprivation category (number and percentage of cases)

Deprivation category	No. of cases	Pathological size ¹				Pathological nodal status ¹			
		T1	T2	T3	Unknown	N0	N1	N0-inadeq	Unknown
Affluent	734	349 (63%)	181 (33%)	24 (4%)	80 (25%)	319 (56%)	230 (40%)	21 (4%)	164 (22%)
2	684	281 (54%)	214 (41%)	30 (6%)	159 (23%)	307 (56%)	220 (40%)	19 (3%)	138 (20%)
3	651	289 (60%)	173 (36%)	18 (4%)	171 (26%)	267 (53%)	215 (42%)	25 (5%)	144 (22%)
4	644	265 (57%)	184 (39%)	18 (4%)	177 (27%)	297 (59%)	186 (37%)	21 (4%)	140 (22%)
Deprived	596	218 (57%)	153 (40%)	14 (4%)	211 (35%)	234 (54%)	190 (44%)	10 (2%)	162 (27%)
Total	3,309	1,402 (58%)	905 (38%)	104 (4%)	898 (27%)	1,424 (56%)	1,041 (41%)	96 (4%)	748 (23%)
Significance		$p=0.072^2$				$p=0.271^2$			

Deprivation category	Clinical size ¹					Clinical nodal status ¹				Metastases ¹		
	T1	T2	T3	T4	Unknown	N0	N1	N2/N3	Unknown	M0	M1	Unknown
Affluent	273 (44%)	239 (38%)	43 (7%)	69 (11%)	110 (15%)	438 (73%)	149 (25%)	17 (3%)	130 (18%)	477 (93%)	37 (7%)	220 (30%)
2	243 (42%)	234 (40%)	48 (8%)	58 (10%)	101 (15%)	431 (74%)	127 (22%)	25 (4%)	101 (15%)	483 (91%)	47 (9%)	154 (23%)
3	239 (42%)	231 (41%)	37 (7%)	56 (10%)	88 (14%)	397 (74%)	123 (23%)	16 (3%)	115 (18%)	433 (93%)	31 (7%)	187 (29%)
4	216 (39%)	218 (40%)	50 (9%)	66 (12%)	94 (15%)	390 (74%)	107 (20%)	29 (6%)	118 (18%)	374 (90%)	43 (10%)	227 (35%)
Deprived	192 (40%)	202 (42%)	32 (7%)	51 (11%)	119 (20%)	307 (73%)	99 (23%)	16 (4%)	174 (29%)	234 (86%)	37 (14%)	325 (55%)
Total	1,163 (42%)	1,124 (40%)	210 (8%)	300 (11%)	512 (15%)	1,963 (73%)	605 (23%)	103 (4%)	638 (19%)	2,001 (91%)	195 (9%)	1,113 (34%)
Significance		$p=0.226^2$				$p=0.019^2$				$p=0.292^2$		

¹ Percentage of women with a known category. For 'unknown' category, percentage of all women

² Significance of association between deprivation category and percentage of women in each category, excluding those in the unknown category

³ Significance of proportion unknown across the deprivation categories

Table 5.4: Women diagnosed with breast cancer in Scotland in 1997: oestrogen receptor (ER) status, grade and histological type by deprivation category (number and percentage of cases)

Deprivation category	No. of cases	ER status ¹			Microscopically verified	Histological type			Grade ¹			
		Negative	Positive	Unknown		Ductal	Lobular	Other	1	2	3/4	Unknown
Affluent	734	145 (25%)	435 (75%)	154 (21%)	711 (97%)	485 (65%)	59 (8%)	190 (25%)	93 (18%)	231 (44%)	204 (39%)	206 (28%)
2	684	157 (27%)	414 (73%)	113 (17%)	661 (97%)	451 (64%)	67 (10%)	166 (24%)	93 (19%)	196 (40%)	202 (41%)	193 (28%)
3	651	141 (27%)	385 (73%)	125 (19%)	626 (96%)	492 (74%)	66 (10%)	156 (24%)	70 (15%)	191 (42%)	197 (43%)	193 (30%)
4	644	120 (23%)	404 (77%)	120 (19%)	614 (95%)	407 (62%)	72 (11%)	165 (25%)	78 (17%)	186 (41%)	185 (41%)	195 (30%)
Deprived	596	151 (33%)	310 (67%)	135 (23%)	562 (94%)	385 (63%)	30 (5%)	181 (30%)	51 (15%)	137 (40%)	154 (45%)	254 (43%)
Total	3,309	714 (27%)	1,948 (73%)	647 (20%)	3,174 (96%)	2,220 (66%)	294 (9%)	858 (26%)	385 (17%)	941 (41%)	942 (42%)	1,041 (31%)
Significance		$p < 0.009^2$		$p = 0.085^1$	$p = 0.061^2$	$p = 0.004^2$			$p = 0.605^2$			$p < 0.001^1$

¹ Percentage of women with a known category. For 'unknown' category, percentage of all women

² Significance of association between deprivation category and percentage of women in each category, excluding those in the unknown category (where applicable)

³ Significance of proportion unknown across the deprivation categories

Among those with known ER status, deprived women were more likely to have ER-negative tumours (33% compared to around 25% in the other deprivation groups).

Diagnosis was microscopically verified for most (96%) women, with no significant difference between the deprivation groups. Overall, 99% of surgical and 77% of non-surgical patients had microscopically verified tumours. Ductal tumours were the most common histological type (66%) followed by lobular carcinomas (9%). There was evidence that the most deprived women were less likely to have lobular carcinomas.

Information on grade was missing for a high proportion (31%) of women, particularly in the deprived group. When only women with known grade were considered, then the deprived women were somewhat more likely to have poorly differentiated tumours (45% compared to 39% of affluent women; $p=0.605$).

Due to the large number of women with missing information on metastatic status, grade and treatment intent, two approaches were adopted in the multivariate analyses: (1) Missing information was treated as an extra category and (2) missing values were imputed (see Chapter 1). Before performing multiple imputation, women whose metastatic status was unknown were re-assigned to the non-metastatic group if their therapy objective was curative (21%) or they were screen-detected (1%). For the remaining 386 (12%) women with unknown metastatic status, multiple imputation was performed using information on age, clinical tumour size and nodal status. The multiple imputation of grade was performed using information on type of surgery, tumour morphology, ER status and imputed metastatic status. The multiple imputation of treatment intent was performed using information on age, surgery, metastatic status and grade.

Screening

The proportion of all women diagnosed as a result of mammographic screening was similar between the deprivation groups (about 18%; Table 5.5). Among women aged 50-64, the proportion was 40%; around 88% of these women attended a specialist cancer centre. This proportion was also similar between the deprivation groups.

Comorbidity

For all three comorbidity measures (see Chapter 1), deprived women had slightly greater comorbidity at the time of cancer diagnosis. The largest difference was seen when comorbidity was measured by the bed-days scale, where 17% of deprived women had spend more than 10 days in hospital in the preceding two years compared to only 12% of women in the other deprivation groups (Table 5.5). There was a gradient across the deprivation groups when comorbidity was measured by the Charlson and Scotland scales, but no clear gradient when measured by the bed-days scale.

Table 5.5: Women diagnosed with breast cancer in Scotland in 1997: screen-detected cancers and comorbidity (number and percentage of cases)

Deprivation category	No. of cases	Screen-detected		Comorbidity			
		All ages	Ages 50-64	Bed-days ¹	Scotland ²	Charlson ³	
Affluent	734	129 (18%)	102 (39%)	85 (12%)	68 (9%)	35 (5%)	
2	684	139 (20%)	115 (42%)	85 (12%)	62 (9%)	36 (5%)	
3	651	113 (17%)	100 (39%)	74 (11%)	71 (11%)	41 (6%)	
4	644	108 (17%)	86 (37%)	80 (12%)	77 (12%)	46 (7%)	
Deprived	596	105 (18%)	95 (41%)	102 (17%)	76 (12%)	57 (10%)	
Total	3,309	594 (18%)	498 (40%)	426 (13%)	354 (11%)	215 (6%)	
Significance ⁴		$p=0.486$		$p<0.001$	$p=0.175$	$p=0.005$	

¹ Greater than 10 inpatient bed-days in the two years prior to the cancer diagnosis

² Any one of certain comorbid conditions recorded in the two years prior to one month after diagnosis (see Chapter 1)

³ Any one of certain comorbid condition recorded in the five years prior to diagnosis (see Chapter 1)

⁴ Chi-square test for association

Treatment

Curative treatment for breast cancer should be available for all women who do not have metastatic disease. This will involve surgery to remove the tumour (from the breast alone or also the lymph nodes) followed by adjuvant systemic therapy and/or radiotherapy¹⁶³. Increasingly, breast conservation (only the lump is excised) as opposed to mastectomy (whole breast is removed) is the preferred option. Breast-conserving surgery has been shown to be as effective as mastectomy when the lymph nodes can be shown not to be involved, whether by axillary clearance, node sampling or, more recently, sentinel node biopsy¹⁶⁴. Breast conservation surgery is usually followed by radiotherapy to the breast or axilla. For women with ER-positive tumours, hormonal treatment (usually tamoxifen) is frequently given. For women with metastases, palliative treatments are given, usually tamoxifen followed by chemotherapy.

The Scottish Intercollegiate Guidelines Network (SIGN) published clinical guidelines for the management of breast cancer in 1998¹⁶⁵, with treatment increasingly being tailored to the tumour characteristics (stage, morphology, grade) and the oestrogen receptor status. Therefore, when investigating the differences in survival between deprivation groups, treatment variations need to be adjusted for differences in tumour characteristics so that causes and relationships can be correctly determined.

Prior to the publication of the SIGN recommendations, and probably as an indirect result of better organisation due to the SNBSP, the 1987 and 1993 breast cancer audits showed increases in the use of radiotherapy (42% to 57%), chemotherapy (8% to 19%) and adjuvant endocrine therapy (66% to 92%) as primary therapy in surgically treated women¹⁶⁶. The proportions of women referred to an oncologist increased from 53% to 64% between 1987 and 1993, but the number of consultant oncologists in Scotland only increased from 32 to 37 over the same period^{22,131}. The number of consultant oncologists rose to 40 in 1997 and 46 in 2000¹⁶⁷.

For women diagnosed in Scotland in 1997, 2 816 (85%) of women received surgery, in whom 1 361 mastectomy and 1 175 breast conservation (BCS) operations were performed within 6 months of diagnosis. Radiotherapy was received by 1 691 (51%) women, chemotherapy by 1 073 (32%) women, and hormone therapy by 2 636 (80%) women (Table 5.6). Among surgically treated women, 1 532 (57%) received radiotherapy, 979 (37%) received chemotherapy and 2 153 (80%) received hormone therapy.

Deprived women were more likely to have a mastectomy (45%) than affluent women (36%) within 6 months of diagnosis, and less likely to have BCS (30% compared to 37%) or radiotherapy (42% compared to 56%). Radiotherapy is the preferred ancillary treatment for BCS, and overall, 82% of women who had BCS received radiotherapy compared to only 35% of women who had a mastectomy. However, deprived women who underwent BCS were still less likely to receive radiotherapy than women from the other deprivation groups who underwent BCS (73% compared to average of 81%; $p=0.039$).

Table 5.6: Women diagnosed with breast cancer in Scotland in 1997: treatment received by deprivation category (number and percentage of cases)

Deprivation category	No. of cases	Surgery				Radiotherapy		Chemotherapy		Hormone Therapy	
		Mastectomy ¹	Breast conservation ¹	Other/unspecified ²	Overall	Within 6 months	Overall	Within 6 months	Overall	Within 6 months	Overall
Affluent	734	263 (36%)	273 (37%)	104 (14%)	640 (87%)	280 (38%)	408 (56%)	232 (32%)	239 (33%)	506 (69%)	594 (81%)
2	684	276 (40%)	256 (37%)	70 (10%)	602 (88%)	262 (38%)	358 (52%)	210 (31%)	221 (32%)	493 (72%)	548 (80%)
3	651	271 (42%)	250 (38%)	39 (6%)	560 (86%)	237 (36%)	339 (52%)	209 (32%)	221 (34%)	469 (72%)	528 (81%)
4	644	281 (44%)	215 (33%)	49 (8%)	545 (85%)	246 (38%)	334 (52%)	189 (29%)	198 (31%)	474 (74%)	522 (81%)
Deprived	596	270 (45%)	181 (30%)	31 (5%)	482 (81%)	153 (26%)	252 (42%)	184 (31%)	194 (33%)	399 (67%)	444 (74%)
Total	3,309	1,361 (41%)	1,175 (36%)	293 (9%)	2,829 (85%)	1,178 (36%)	1,691 (51%)	1,024 (31%)	1,073 (32%)	2,341 (71%)	2,636 (80%)
Significance ³		p=0.003			p=0.003	p<0.001	p<0.001	p=0.839	p=0.816	p=0.082	p=0.015

¹ If received within 6 months of diagnosis (Mastectomy: 95% within 6 months; BCS: 90% within 6 months)

² Other surgery includes breast conservation and mastectomy performed more than 6 months after diagnosis (77 and 64 women respectively), and cases where the woman had surgery but the type of surgery is not known (152 women)

³ Chi-square test for association

For those women who did receive radiotherapy, women who had a mastectomy received radiotherapy at a longer time since diagnosis than women who had BCS. Overall, 81% of women who had BCS received their radiotherapy within 6 months of diagnosis compared to 55% of women who had a mastectomy. Of women who were irradiated, deprived women were less likely to receive radiotherapy within 6 months of diagnosis, whether they underwent BCS (71% compared to 79% in affluent women) or mastectomy (43% compared to 47% in affluent women).

The decision to treat a woman with BCS instead of a mastectomy was correlated with tumour size, nodal status and grade. Women were more likely to receive BCS if they had node negative tumours (54% of women with pN0 tumours, 30% with pN1, and 47% with pN0_{inadequate}), small tumours (57% with pT1, 31% with pT2, and 13% with pT3), and low grade tumours (58% with grade 1, 43% with grade 2, and 39% with grade 3+). The T and N proportions were similar when assessed using clinical stage information.

Half (50%) of the women with tumours directly extending to the chest wall or skin (stage cT4) did not have surgery. Women receiving surgery at a regional RT centre were more likely to receive BCS than those treated elsewhere (51% compared to 42% of those treated at other high-workload hospitals and fewer at medium- and low-workload hospitals; Table 5.7). This effect was seen both for women diagnosed by screening and those presenting with clinical disease, and was seen in subsets of women with the same pathological tumour size (pT1, pT2 or pT3) at presentation (data not shown).

Of women without metastases at diagnosis, 9% did not have surgery. Of these women, 64% were elderly (aged over 75) or had comorbidity (21%, compared to only 13% of whole group). Some women may have refused surgery.

Chemotherapy was given before surgery for 201 (6%) women, most probably to reduce tumour size. Adjuvant endocrine therapy (tamoxifen or ovarian ablation) was given to 80% of all women, but deprived women were less likely to receive this treatment (74% compared to 81% of women in the affluent group; Table 5.6). Women with ER-positive tumours were significantly more likely to receive adjuvant endocrine therapy than those with ER-negative tumours (90% compared to 55%; $p < 0.001$). However, this did not explain the deprivation-specific differences: deprived women were less likely to receive adjuvant endocrine therapy

with both ER-negative (49% compared to 57% of affluent women; $p=0.440$) and ER-positive (90% compared to 94%; $p=0.157$) tumours.

Table 5.7: Women diagnosed with breast cancer in Scotland in 1997: hospital of surgery and type of surgery (number and percentage of cases)

Hospital of surgery	Mastectomy	BCS	Other, unspecified ¹	None
Regional RT centre	544 (44%)	632 (51%)	53 (4%)	211 (15%)
High-workload hospital	358 (56%)	269 (42%)	11 (2%)	73 (10%)
Medium-high workload hospital	352 (57%)	248 (40%)	20 (3%)	101 (14%)
Medium-low workload hospital	126 (51%)	81 (33%)	39 (16%)	41 (14%)
Low-workload hospital	45 (49%)	22 (24%)	25 (27%)	34 (27%)
Did not attend a hospital	0 (0%)	0 (0%)	0 (0%)	24 (100%)
Total	1,425 (43%)	1,252 (38%)	148 (4%)	484 (15%)

Chi-square test for association between hospital and surgery type: $p<0.001$

¹ Other surgery includes cases where the woman had surgery but the type of surgery is not known.

Women seen by high-workload clinicians were more likely to receive chemotherapy (40% of women compared to 31% for those seen by medium-workload and 7% by low-workload clinicians), and less likely to receive hormone therapy (78% compared to 82% for both medium- and low-workload clinicians). Previous research in Scotland had shown an increase of both chemotherapy and hormone therapy for women treated by high-workload clinicians²².

Women who were treated with curative intent were more likely to receive surgery (98% compared to 44% of women whose treatment intent was palliative), and radiotherapy (56% compared to 39%), and had a similar likelihood of receiving chemotherapy (33% compared to 29%) or hormone therapy (81% compared to 79%). Younger patients were also more likely to receive surgery (97% of women aged <50 compared to 35% of women aged 80+). Of the non-surgical patients, 82% received hormone therapy (89% of women with ER-negative tumours and 77% with ER-positive tumours), 11% received chemotherapy and 18% received radiotherapy. The use of hormone therapy was lower than observed in an audit of Yorkshire women diagnosed 1988-92, where 95% of women not treated surgically received hormone therapy, 7% received chemotherapy and 20% received radiotherapy¹⁴⁰.

Two-year survival

Univariate analyses

Factors which had an influence on differences in 2-year survival between deprivation categories were investigated in a Cox proportional hazards regression model. With the initial model (deprivation only) the relative risk of death within two years of diagnosis was substantially raised (RR = 1.65 (95% CI: 1.27-2.14); $p < 0.001$) among deprived compared with affluent women. None of the factors reflecting access to health care, patient or tumour characteristics, and treatment, reduced the relative risk of death between deprived and affluent women below 1.3 or rendered this risk non-significant (see columns 1 to 4 of Table 5.8). The exception to this was when the women with unknown metastatic status were excluded from the analysis; however, the excluded women have a biased distribution with respect to deprivation (see Table 5.3). All of the factors, with the exception of urban indicator, health board of residence and radiotherapy provision, were important in predicting survival and improved the fit of the model compared to the null model including deprivation group and age (see column 5 of Table 5.8).

Patient characteristics

Survival was strongly related to age, with significantly poorer survival at two years after diagnosis for women aged 75 and over (61% compared to 89% for those aged under 75). The poorest survival was in those aged over 85 years. Including age in the model significantly improved the model fit but did not explain the difference in survival between affluent and deprived, only reducing the relative risk of death from 1.65 to 1.60. Survival was similar for urban and rural residents, and this did not vary within deprivation groups. Including the urban indicator in the model, therefore, did not improve the model fit. Survival varied across the health boards, being highest in Fife and lowest in Forth Valley. The differences in survival between health boards were not significant after adjusting for age. This has been noted previously for women diagnosed with breast cancer in Scotland during 1991-95¹.

Comorbidity was strongly related to survival even after adjustment for age. Women who spent more than 10 days in hospital in the two years prior to diagnosis had poorer survival than those who spent with fewer than 5 or no days in hospital (53% compared to 87%; $p < 0.001$).

Table 5.8: Women diagnosed with breast cancer in Scotland in 1997: univariate influence of individual factors on the relative risk of death within two years of diagnosis among deprived compared to affluent women (Cox proportional hazards regression analysis)

Variable included in the model ¹	Relative risk ²	95% CI Low High		P-value ³	P-value of added term ⁴
Initial model: Deprivation category	1.65	1.27	2.14	<0.001	-
Patient characteristics:					
Age (null model) ⁵	1.60	1.23	2.07	<0.001	<0.001
Health board of residence	1.73	1.30	2.31	<0.001	0.458
Urban indicator	1.54	1.18	2.02	<0.01	0.248
Bed-days comorbidity score	1.60	1.23	2.08	<0.001	<0.001
Charlson comorbidity score	1.61	1.24	2.09	<0.001	<0.001
Scotland comorbidity score	1.63	1.26	2.11	<0.001	<0.001
Health care system factors:					
Attended a high workload hospital?	1.57	1.21	2.04	<0.01	<0.001
Treated at a high workload hospital?	1.56	1.20	2.02	<0.01	<0.001
Attended a specialist department	1.51	1.16	1.96	<0.01	<0.001
Emergency admission	1.57	1.21	2.04	<0.01	<0.001
Time from diagnosis to definitive treatment	1.58	1.20	2.08	<0.01	<0.001
Number of hospitals attended	1.65	1.27	2.14	<0.001	<0.001
Number of hospital from home visits	1.58	1.22	2.06	<0.01	<0.001
Consultant workload	1.58	1.22	2.05	<0.01	<0.001
Screen detected (yes/no)	1.61	1.24	2.08	<0.001	<0.001
Tumour characteristics:					
Microscopic verification	1.58	1.22	2.04	<0.01	<0.001
Ductal, lobular or other	1.53	1.18	1.98	<0.01	<0.001
Pathological T size	1.36	1.05	1.76	0.021	<0.001
Pathological N status	1.48	1.15	1.93	<0.01	<0.001
Clinical T stage	1.63	1.26	2.12	<0.001	<0.001
Clinical N stage	1.51	1.16	1.96	<0.01	<0.001
Metastatic status ⁶	1.33	1.02	1.73	0.033	<0.001
Metastatic status ⁷	1.39	0.95	2.02	0.087	<0.001
Metastatic status ⁸	1.34	1.03	1.73	0.029	<0.001
Grade ⁶	1.36	1.05	1.76	0.021	<0.001
Grade ⁷	1.95	1.27	2.99	<0.01	<0.001
Grade ⁸	1.56	1.21	2.03	<0.01	<0.001
ER status	1.50	1.16	1.95	<0.01	<0.001
Treatment factors:					
Therapy objective (curative or palliative) ⁶	1.58	1.22	2.05	<0.01	<0.001
Therapy objective ⁸	1.34	1.03	1.74	0.027	<0.001
Surgery (yes/no; no time restriction)	1.36	1.05	1.77	0.021	<0.001
Surgery (yes/no; within 6 months)	1.63	1.26	2.12	<0.001	<0.001
Radiotherapy (yes/no)	1.59	1.22	2.06	<0.01	0.123
Chemotherapy (yes/no)	1.61	1.24	2.08	<0.001	<0.001
Hormone therapy (yes/no)	1.58	1.22	2.04	<0.01	<0.001

¹ Each categorical variable is added separately to the null model containing deprivation category and age

² Relative risk of death in the deprived compared to affluent group

³ Significance of the difference in the relative risk

⁴ Improvement in model fit when each categorical variable is added to the null model

⁵ The significance of the age term is tested against the initial model containing only deprivation category

⁶ Unknowns included as a separate category

⁷ Women with unknown values excluded from the analysis

⁸ Unknowns imputed (see Chapter 1)

Increasing comorbidity on the Charlson scale was associated with decreasing survival (85% for no comorbidity, 60% if 1-2 comorbid conditions, and 36% if 3+ comorbid conditions; $p<0.001$). Any comorbidity compared to no comorbidity was also associated with reduced survival using the Scottish scale (64% compared to 85%; $p<0.001$). Survival for women with comorbidity as measured by the Charlson index was significantly poorer for deprived women than those in the other deprivation groups (37% compared to an average of 61%; $p<0.01$).

Health care system factors

Women who attended a regional RT centre or other high-workload hospital at some point during their cancer spell had the best two-year survival (86% compared to 70% for those attending medium-high and medium-low workload hospitals, and 65% for those attending low-workload hospitals). Survival was very poor for women who did not attend a hospital (5%; $p<0.001$).

Women whose main treatment was received in a regional RT centre or other high-workload hospital had better survival (92%) than those treated in medium-high workload (88%), medium-low workload (85%) or low-workload (87%) hospitals. Women who attended a specialist department within three months of diagnosis had significantly better survival than women who attended a specialist department later or who did not attend one at all (88% compared to 56%; $p=0.002$). The three factors relating to hospital workload and specialty all improved the model fit when added to the null model, but did not explain the deprivation-specific gradient in survival (Table 5.8).

Women who presented as an emergency admission had poorer survival than women who were admitted routinely (45% compared to 87%; $p<0.001$), and deprived women were more likely to present as an emergency. However, inclusion of type of admission only reduced the relative risk of death among deprived compared to affluent women from 1.65 to 1.57.

Women who waited less than two weeks between diagnosis and surgery (or other treatment for non-surgical patients) had poorer survival than women who had a longer wait (76% compared to 87%; $p<0.001$). Women who presented as an emergency were more likely to have a short wait (45% compared to 21% of non-emergency admissions); however, the difference in survival was seen for both women admitted as an emergency and those

admitted routinely. The difference in survival is accounted for by the distribution of tumour characteristics (size, nodal status, metastatic status and grade) at diagnosis. Among women who attended hospital during their cancer spell, survival was better for women who attended more hospitals, and those who had the most visits to hospital between diagnosis and definitive treatment. Again, this appeared to be due to women with better prognosis attending more hospitals and being less likely to be retained in hospital on first admission. Survival was significantly worse for deprived patients who attended only one hospital (75% compared to 84% for affluent patients; $p < 0.05$). These three health care system factors may be related to comorbidity.

Women who were seen by a consultant with a medium- or high-workload had similar two-year survival (88%), but women seen by a low-workload consultant had poorer survival (59%), as did those women who did not see a consultant or for whom the consultant details were not recorded (64%). Seeing a high-workload consultant was more important for women treated with palliative intent (survival at two years of 57%, compared to 41% for medium-workload and 35% for low-workload consultants; and 45% if consultant workload was not recorded) than those treated with curative intent (95% for high-workload, 94% for medium-workload, 90% for low-workload consultants; and 92% if the consultant workload was not recorded).

As would be expected, women aged 50-69 with screen-detected cancers had significantly better survival at two years after diagnosis than those who were not screen-detected (98% compared to 87%; $p < 0.001$). Whether the woman's tumour was microscopically verified was also very strongly related to survival (86% compared to 17% at two years) and this was not accounted for by age. Survival was similar for women with ductal and lobular tumours despite previous research indicating that lobular carcinomas confer a better prognosis¹³³. Survival was worse for women with other or unknown histological type, and this was because a higher proportion of women with other or unknown type were being treated with palliative intent (45% compared to 17% of women with ductal or lobular tumours).

Tumour characteristics

Two-year survival was significantly better for women with small tumours (for clinical size: 94% for women with cT1 tumours, 86% for cT2, 71% for cT3 and 56% for cT4; and for pathological size: 96% for pT1, 87% for pT2 and 68% for pT3), tumours with no nodal

involvement (for clinical nodal status, 91% for cN0, 76% for cN1 and 45% for cN2/3; and for pathological nodal status, 96% for pN0, 86% for pN1 and 95% for pN_{inadequate}), and non-metastatic tumours (91% for M0, 42% for M1). The relative risk of death between affluent and deprived women was non-significant when women with unknown metastases were included as a separate category in the analyses, but significant when metastatic status was imputed (Table 5.8). When only women with metastatic disease were considered, survival was significantly better for affluent compared to deprived women; when only women with non-metastatic disease were considered, the difference in survival between the deprivation groups was no longer significant if women with imputed non-metastatic disease were included.

Within each tumour grade, survival was similar across the deprivation groups, except for Grade III tumours, where there was a clear gradient of poorer survival with increasing deprivation. Women with grade I tumours had the most favourable prognosis (92%, compared to 87% for grade 2, and 75% for grade 3-4 tumours). Women with unknown grade had significantly poorer survival than those with known grade, because they were more likely to be treated with palliative intent. The deprivation-specific differences in survival remained whichever way the unknown grade information was dealt with (separate category, excluded or imputed).

Survival was poorer for ER-negative than ER-positive tumours (80% compared to 92%). Women with unknown ER status had significantly poorer survival than those with known ER status (60%), which was accounted for by these women being more likely to have treatment with palliative or unknown intent.

Treatment factors

None of the treatment variables independently accounted for differences in two-year survival between the deprivation categories. Overall, survival was better for women who had BCS compared to mastectomy (93% compared to 89%; $p < 0.01$) and significantly poorer for women who received other/unknown or no surgery (48%). The difference in survival by mastectomy or BCS was reduced and non-significant when an adjustment was made to account for differences in the distribution of age and pathological tumour stage. Survival from BCS was similar across the deprivation groups, but for women receiving a mastectomy, survival significantly decreased with increasing deprivation.

Women receiving radiotherapy had a significantly more favourable outlook than those who did not (87% compared to 78%; $p < 0.001$), although this was largely accounted for by differences in the distribution of age. Time to radiotherapy (≤ 6 months compared to > 6 months) did not appear to influence survival. Women who received chemotherapy within 6 months of diagnosis had higher survival at two years after diagnosis than those who did not receive chemotherapy (87% compared to 81%; $p < 0.001$). This effect was enhanced when differences in the age distribution were taken into account. Women who received chemotherapy more than 6 months after diagnosis had significantly poorer survival (55%; $p < 0.001$), and this difference was evident for women treated with curative and palliative intent. The benefit of chemotherapy varied significantly between deprivation groups.

Women who received hormone therapy more than 6 months after diagnosis, conversely, had significantly higher survival than those receiving hormone therapy within 6 months of diagnosis (92% compared to 83%; $p < 0.001$), however this was again due to differences in the age distribution. Clinical trials predict a 3.5% survival advantage at five years for adjuvant systemic treatment^{16a}, and in the data presented here there was a significant survival advantage at two years after diagnosis for women who received hormone therapy (84% compared to 76% for women who did not receive hormone therapy; $p < 0.001$) which was not accounted for by age. Survival varied by deprivation group for women receiving hormone therapy, with 81% of deprived compared to 86% of affluent women still alive two years after diagnosis. For women not receiving hormone therapy the gradient was larger (68% compared to 79%), resulting in a significant interaction between deprivation group and hormone therapy. However, differences in the provision of and survival from hormone therapy did not account for the difference in survival by deprivation group (RR reduced from 1.65 to 1.58; Table 5.8).

Multivariate analysis

The multivariate analysis was performed in two stages. Firstly the factors were modelled in groups to identify the most important factors relating to patient characteristics, service and presentation characteristics, and treatment. Deprivation category and age group were included in each model. Secondly, the significant variables in each group model were combined in a further model to identify the most important prognostic indicators overall,

and their effect on the deprivation-specific differences (Table 5.9). Backward selection procedures were used.

If only deprivation is included in the model (model 0) then the relative risk (RR) of death at two years after diagnosis for deprived compared to affluent women was 1.65 ($p < 0.001$). In model 1, when factors relating to the patient were added to the model, age and the bed-days comorbidity score were significant prognostic indicators. Addition of age and bed-days score to the model only reduced the RR from 1.65 to 1.60, thus not explaining the differences in survival between deprivation groups. Health board of residence, urban indicator, Charlson comorbidity score and Scotland comorbidity score were not important factors in the model when age and bed-days comorbidity score were present.

Model 2 looked at the health care system factors, and identified the hospital of treatment, consultant workload, type of admission (emergency or routine), number of visits to hospital between diagnosis and treatment, and whether the woman was screen-detected as important explanatory variables. Addition of these variables to the model increased the RR from 1.65 to 1.71. Conditional on these variables being in the model, information on time from diagnosis to treatment, number of hospitals attended overall, whether attended a high-workload hospital at some point during the cancer spell, and whether they were seen in a specialist department did not improve the fit of the model in explaining survival differences.

The time from diagnosis to treatment variable was a significant explanatory variable, but was not included in the model because it was the group of women whose time interval was categorised as unknown, who had significantly different survival to those with a time recorded; these comprise largely of patients who did not receive treatment and so is, in effect, a measure of treatment provision.

Model 3 looked at the presentation factors, with unknown grade and metastatic status either included as a separate category (columns 2-5) or imputed (columns 6-9). All the presentation factors with the exception of age were important prognostic indicators, and the same pattern of effect was seen for all factors whichever method of dealing with the unknowns was used.

Table 5.9: Women diagnosed with breast cancer in Scotland in 1997: multivariate influence of variables on the relative risk of death within two years of diagnosis among deprived compared to affluent women (Cox proportional hazards regression analysis)

Model Variables included in the model	Unknowns ¹ as separate group			Unknowns ¹ imputed		
	Relative risk	95% CI Low High	P-value	Relative risk	95% CI Low High	P-value
Model 0: Null model						
Dep1: Affluent	1.00			-		
Dep2	1.06	0.81 1.40	0.675	-		
Dep3	1.28	0.98 1.67	0.075	-		
Dep4	1.40	1.08 1.82	0.012	-		
Dep5: Deprived	1.65	1.27 2.14	<0.001	-		
Model 1: Patient characteristics						
Dep1: Affluent	1.00			-		
Dep2	1.08	0.82 1.42	0.589	-		
Dep3	1.33	1.01 1.73	0.040	-		
Dep4	1.50	1.15 1.95	<0.01	-		
Dep5: Deprived	1.60	1.23 2.08	<0.001	-		
Ages 20-34	1.00			-		
Ages 35-49	0.64	0.31 1.29	0.210	-		
Ages 50-59	0.58	0.29 1.17	0.129	-		
Ages 60-69	0.87	0.44 1.73	0.691	-		
Ages 70-74	1.44	0.72 2.88	0.306	-		
Ages 75-79	1.82	0.91 3.63	0.089	-		
Ages 80-84	2.55	1.27 5.11	<0.01	-		
Ages 85+	3.75	1.89 7.46	<0.001	-		
No bed-days comorbidity	1.00			-		
1-4 bed-days comorbidity	0.93	0.73 1.20	0.594	-		
5-10 bed-days comorbidity	1.23	0.94 1.63	0.135	-		
11+ bed-days comorbidity	2.89	2.35 3.56	<0.001	-		
Model 2: Health care system factors²						
Dep1: Affluent	1.00			-		
Dep2	1.10	0.83 1.47	0.496	-		
Dep3	1.27	0.96 1.69	0.095	-		
Dep4	1.46	1.11 1.91	<0.01	-		
Dep5: Deprived	1.71	1.31 2.25	<0.001	-		
Treated at third visit	1.00			-		
Treated at second visit	0.44	0.26 0.73	<0.01	-		
Treated at first visit	0.70	0.44 1.11	0.130	-		
Treated at a regional RT centre	1.00			-		
Treated in a high workload hospital	0.55	0.42 0.72	<0.001	-		
Treated in a med-high workload hosp	0.80	0.64 1.01	0.064	-		
Treated in a med-low workload hosp	0.84	0.63 1.13	0.257	-		
Treated in a low workload hospital	1.00	0.68 1.48	0.989	-		
Did not attend a hospital	3.56	2.08 6.10	<0.001	-		
Low-workload consultant	1.00			-		
Medium-low workload consultant	0.66	0.48 0.91	0.012	-		
Medium-high workload consultant	0.59	0.45 0.78	<0.001	-		
High-workload consultant	0.61	0.43 0.85	<0.01	-		
Unknown consultant workload	0.79	0.61 1.03	0.079	-		
Routine admission	1.00			-		
Emergency admission	2.61	2.09 3.26	<0.001	-		
Unknown admission type	1.02	0.51 2.04	0.965	-		
Screen-detected	1.00			-		
Not screen-detected	4.26	2.57 7.05	<0.001	-		

Table 5.9 continued

Model Variables included in the model	Unknowns ¹ as separate group				Unknowns ¹ imputed			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 3: Presentation factors								
Dep1: Affluent	1.00				1.00			
Dep2	1.00	0.76	1.33	0.977	0.98	0.74	1.30	0.899
Dep3	1.25	0.95	1.63	0.109	1.28	0.98	1.67	0.073
Dep4	1.14	0.87	1.49	0.352	1.13	0.86	1.48	0.379
Dep5: Deprived	1.29	0.99	1.68	0.058	1.33	1.02	1.73	0.034
Histologically verified	1.00				1.00			
Not histologically verified	2.57	1.99	3.32	<0.001	2.42	1.87	3.13	<0.001
Ductal	1.00				1.00			
Lobular	0.96	0.66	1.40	0.826	0.94	0.64	1.36	0.730
Other/unknown	1.27	1.02	1.57	0.033	1.29	1.04	1.59	0.018
Stage pT1	1.00				1.00			
Stage pT2	1.89	1.33	2.68	<0.001	1.93	1.36	2.75	<0.001
Stage pT3	2.28	1.40	3.73	<0.01	2.32	1.42	3.81	<0.01
Pathological T stage unknown	1.92	1.35	2.72	<0.001	1.82	1.27	2.60	<0.01
Stage pN0	1.00				1.00			
Stage pN1	2.34	1.67	3.29	<0.001	2.18	1.54	3.07	<0.001
Stage pN0 inadequate sample	1.37	0.54	3.43	0.507	1.36	0.54	3.40	0.516
Pathological N stage unknown	6.95	4.85	9.95	<0.001	5.98	4.14	8.62	<0.001
Stage cT1	1.00				1.00			
Stage cT2	1.20	0.88	1.63	0.248	1.23	0.90	1.67	0.194
Stage cT3	1.30	0.88	1.92	0.185	1.40	0.95	2.06	0.093
Stage cT4	1.64	1.17	2.31	<0.01	1.70	1.21	2.40	<0.01
Clinical T stage unknown	1.51	1.09	2.09	0.013	1.59	1.15	2.21	<0.01
Stage cN0	1.00				1.00			
Stage cN1	1.43	1.12	1.84	<0.01	1.47	1.15	1.89	<0.01
Stage cN2/3	1.93	1.35	2.76	<0.001	2.17	1.54	3.05	<0.001
Clinical N stage unknown	1.02	0.78	1.33	0.869	0.90	0.70	1.16	0.407
No metastases	1.00				1.00			
Metastases	2.74	2.09	3.59	<0.001	2.61	2.11	3.22	<0.001
Metastatic status unknown	1.46	1.16	1.85	<0.01	-			
Grade 1	1.00				-			
Grade 2	1.86	1.00	3.44	0.050	-			
Grade 3-4	2.60	1.42	4.75	<0.01	-			
Grade unknown	2.49	1.37	4.54	<0.01	-			
ER -ve	1.00				1.00			
ER +ve	0.43	0.34	0.55	<0.001	0.41	0.32	0.51	<0.001
ER status unknown	0.61	0.47	0.80	<0.001	0.55	0.42	0.71	<0.001
Model 4: Treatment factors								
Dep1: Affluent	1.00				1.00			
Dep2	1.08	0.82	1.43	0.577	1.07	0.81	1.40	0.655
Dep3	1.22	0.93	1.60	0.151	1.14	0.87	1.49	0.339
Dep4	1.35	1.04	1.76	0.026	1.24	0.96	1.62	0.105
Dep5: Deprived	1.37	1.05	1.78	0.020	1.24	0.95	1.61	0.109
Curative treatment intent	1.00				1.00			
Palliative treatment intent	6.97	5.39	9.01	<0.001	6.94	5.46	8.81	<0.001
Unknown treatment intent	4.17	3.13	5.55	<0.001	-			
Mastectomy	1.00				1.00			
BCS	0.65	0.50	0.84	<0.01	0.66	0.51	0.86	<0.01
Other or unknown surgery	3.25	2.56	4.13	<0.001	1.31	0.79	2.18	0.295
No surgery performed	1.31	0.80	2.15	0.286	2.63	2.06	3.36	<0.001
No chemotherapy	1.00				1.00			
Chemo within 6 months	0.82	0.65	1.03	0.089	0.86	0.68	1.08	0.200
Chemo > 6 months	2.24	1.44	3.47	<0.001	2.21	1.42	3.43	<0.001
Unknown chemotherapy details	0.78	0.26	2.31	0.649	1.10	0.37	3.26	0.859

Table 5.9 continued

Model Variables included in the model	Unknowns ¹ as separate group				Unknowns ¹ imputed			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 4 continued..								
No hormone therapy	1.00				1.00			
Hormone therapy within 6 months	0.44	0.35	0.54	<0.001	0.45	0.37	0.56	<0.001
Hormone therapy > 6 months	0.37	0.24	0.58	<0.001	0.41	0.27	0.63	<0.001
Unknown Hormone therapy details	0.67	0.28	1.59	0.367	0.66	0.29	1.54	0.338
Model 5: Final model								
Dep1: Affluent	1.00				1.00			
Dep2	0.93	0.70	1.23	0.594	0.97	0.73	1.29	0.820
Dep3	1.26	0.96	1.66	0.095	1.27	0.96	1.67	0.091
Dep4	1.20	0.91	1.59	0.191	1.17	0.89	1.55	0.256
Dep5: Deprived	1.36	1.04	1.79	0.026	1.35	1.03	1.77	0.030
No bed-days comorbidity	1.00				1.00			
1-4 bed-days comorbidity	1.14	0.88	1.47	0.311	1.11	0.86	1.43	0.438
5-10 bed-days comorbidity	1.26	0.95	1.67	0.110	1.30	0.98	1.72	0.069
11+ bed-days comorbidity	1.74	1.40	2.15	<0.001	1.76	1.42	2.18	<0.001
Screen-detected	1.00				1.00			
Not screen-detected	2.04	1.23	3.39	<0.01	2.14	1.29	3.55	<0.01
Treated in a regional RT centre	1.00				1.00			
Treated in a high-workload hospital	0.72	0.54	0.95	0.019	0.71	0.54	0.93	0.012
Treated in a med-high workload hosp	1.10	0.87	1.39	0.427	1.07	0.85	1.34	0.556
Treated in a med-low workload hosp	1.17	0.87	1.57	0.287	1.21	0.90	1.61	0.203
Treated in a low-workload hospital	1.14	0.78	1.68	0.501	1.09	0.74	1.60	0.665
Did not attend a hospital	3.59	2.18	5.91	<0.001	2.96	1.82	4.81	<0.001
Histologically verified	1.00				1.00			
Not histologically verified	1.77	1.33	2.35	<0.001	1.84	1.39	2.44	<0.001
Stage pT1	1.00				1.00			
Stage pT2	1.62	1.13	2.33	<0.01	1.72	1.20	2.46	<0.01
Stage pT3	1.87	1.13	3.11	0.016	1.96	1.18	3.25	<0.01
Pathological T stage unknown	1.12	0.75	1.67	0.573	1.13	0.76	1.69	0.555
Stage pN0	1.00				1			
Stage pN1	1.95	1.37	2.78	<0.001	1.92	1.34	2.74	<0.001
Stage pN0 inadequate sample	1.33	0.53	3.35	0.540	1.28	0.51	3.22	0.597
Pathological N stage unknown	3.05	2.01	4.62	<0.001	3.07	2.02	4.65	<0.001
Stage cT1	1.00				1.00			
Stage cT2	1.05	0.77	1.44	0.743	1.08	0.79	1.48	0.624
Stage cT3	1.22	0.82	1.81	0.320	1.35	0.91	1.99	0.138
Stage cT4	1.45	1.03	2.06	0.034	1.55	1.10	2.19	0.012
Clinical T stage unknown	1.55	1.11	2.17	0.010	1.65	1.18	2.30	<0.01
Stage cN0	1.00				1.00			
Stage cN1	1.27	0.99	1.64	0.060	1.39	1.08	1.78	0.010
Stage cN2/3	1.63	1.14	2.35	<0.01	1.98	1.40	2.79	<0.001
Clinical N stage unknown	0.96	0.73	1.26	0.762	0.94	0.73	1.23	0.673
No metastases	1.00				1.00			
Metastases	2.50	1.89	3.30	<0.001	1.66	1.32	2.09	<0.001
Unknown metastatic status	1.55	1.21	1.99	<0.01	-			
Grade 1	1.00				-			
Grade 2	2.00	1.07	3.73	0.029	-			
Grade 3-4	2.79	1.52	5.12	<0.01	-			
Unknown Grade	2.38	1.30	4.35	<0.01	-			
ER -ve	1.00				1.00			
ER +ve	0.49	0.38	0.63	<0.001	0.47	0.37	0.61	<0.001
ER status unknown	0.56	0.43	0.74	<0.001	0.57	0.43	0.74	<0.001
Curative treatment intent	1.00				1.00			
Palliative treatment intent	3.55	2.69	4.67	<0.001	3.18	2.42	4.20	<0.001
Unknown treatment intent	2.80	2.07	3.79	<0.001	-			

Table 5.9 continued

Model Variables included in the model		Unknowns ¹ as separate group			Unknowns ¹ imputed				
		Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
			Low	High			Low	High	
Model 5 continued..									
Mastectomy		1.00				1.00			
BCS		0.98	0.75	1.30	0.907	1.02	0.77	1.35	0.902
Other or unknown surgery details		1.63	1.15	2.32	<0.01	1.47	1.03	2.10	0.033
No surgery performed		0.92	0.55	1.55	0.765	1.03	0.60	1.76	0.927
No chemotherapy		1.00				1.00			
Chemo within 6 months		0.63	0.48	0.82	<0.01	0.75	0.58	0.97	0.029
Chemo > 6 months		1.97	1.24	3.11	<0.01	2.27	1.44	3.59	<0.001
Unknown chemotherapy details		0.70	0.22	2.22	0.546	0.86	0.25	2.99	0.811
No hormone therapy		1.00				1.00			
Hormone therapy within 6 months		0.51	0.41	0.64	<0.001	0.55	0.44	0.68	<0.001
Hormone therapy > 6 months		0.42	0.27	0.64	<0.001	0.46	0.30	0.71	<0.001
Unknown Hormone therapy details		0.72	0.29	1.79	0.481	0.85	0.32	2.24	0.743

¹ Includes unknown metastatic status, grade and treatment intent

² Age was also significant in this model but the estimates are not presented on the table.

Grade was no longer significant when values were imputed, which may be because the imputation was based on four factors, three of which were in this model. These models explained around half the difference in survival between affluent and deprived women. When the unknowns were included as a separate category the RR was reduced from 1.65 to 1.29 and was not significant. However, the distribution of missing data is biased which makes interpretation complicated. When the unknowns were imputed, the RR was reduced to 1.33, and the difference was marginally significant. The trend across the deprivation groups was less clear with model 3.

In model 4, treatment factors relating to treatment intent (palliative or curative), surgery provision and type, chemotherapy provision and timing and hormone therapy provision and timing, were all important in determining survival outcome. Age and radiotherapy were not significantly related to survival in a model containing the other factors. In the model where women with unknown treatment intent were included as a separate category, around half the difference in survival between affluent and deprived was explained (RR=1.37; $p=0.020$). When unknown treatment intent was imputed, the treatment model explained around two-thirds of the difference in risk of death between affluent and deprived women (RR reduced from 1.65 to 1.24) and the difference was non-significant.

Finally, model 5 was fitted including all the factors found to be important prognostic indicators in the sub-group models (1-4). The model with the unknowns included as a separate category was very similar to the model with values imputed, the exception being

grade which was no longer significant when imputed. Overall, these models explained around half the difference in survival between affluent and deprived women ($RR=1.35-1.36$), but the difference was significant despite the larger variation that had been explained by some of the sub-groups models. The important prognostic factors in the final model were bed-days comorbidity, whether screen-detected, hospital of treatment, whether the tumour was histologically verified, pathological T and N stage, clinical T and N stage, metastatic status, grade, oestrogen receptor status, treatment intent, type and timing of surgery, and provision and timing of chemotherapy and hormone therapy.

Discussion

These analyses show that deprived women compared with affluent women had more comorbidity at diagnosis, were more likely to present with metastatic disease and have ER negative tumours, and less likely to have lobular carcinomas. Deprived women were also more likely to present as an emergency and to stay in hospital after first admission; they were less likely to attend a regional RT centre or specialist department, less likely to see a high-workload clinician, and more likely to receive a mastectomy, and less likely to receive adjuvant radiotherapy, regardless of the surgical intervention. Deprived women were also less likely to receive hormone therapy, whether their tumour was ER negative or ER positive. Indeed, deprived women with breast cancer appear to be consistently worse off than affluent women throughout their cancer journey.

Differences in tumour characteristics at diagnosis, particularly metastatic status, appear to be the most influential in explaining the differences in survival between deprivation groups when looked at in isolation, although the picture is less clear when these factors are considered together with the hospital and treatment factors. The widely varying treatment offered to women with breast cancer across Scotland also appears to be to explain some of the differences in survival, and relates to the hospital they attend and the consultant who sees them.

An audit of Scottish women diagnosed with breast cancer in 1987²² found that a survival advantage for affluent women disappeared in their multivariate analyses, and around a third of the survival difference was accounted for by the higher proportion of ER-negative tumours in the deprived women who underwent surgery. The authors also found an

influence of health board of first treatment for the surgically treated women, particularly those aged under 75 at diagnosis, which appeared to be due to differences in the use of adjuvant systemic therapy. The analyses for women diagnosed in Scotland in 1997 also identified deprived women as having a higher proportion ER-negative tumours, and this appeared to account for up to a quarter of the deprivation-specific survival differences. Differences in the use of adjuvant systemic therapy were also still clearly evident, despite a 10-year period having elapsed, during which time breast cancer services were re-organised as a result of the introduction of the national breast screening programme.

It is encouraging that the 1987 audit, 1993 audit and these routine data for 1997 show progressively increasing use of radiotherapy, chemotherapy and hormonal treatments. The proportion of women receiving breast conserving therapy rather than a mastectomy is also increasing, with 47% of surgically-treated women diagnosed in 1997 receiving breast-conserving surgery²² compared to 40% of women diagnosed in 1987. From trial data, treatment with breast-conserving surgery should not confer a survival benefit compared to mastectomy, so the differences in surgical interventions between the deprivation groups should not translate into a survival benefit; however, it may have a large impact on quality of life and speed of recovery¹⁶⁴. In 1997, 44% of surgically-treated women underwent surgery at a regional RT centre, 23% at other high-workload hospitals (treating more than 104 patients per annum; highest workload quartile), 22% at medium-workload hospitals (56-104 patients) and 12% at low-workload hospitals (<56 patients). The regional RT centres were more likely to perform breast-conserving surgery (51% of patients) than the other high-workload (42%), the medium-high workload (40%) or the medium-low and low-workload (30%) hospitals. This difference was seen for screen-detected and non screen-detected women, and for women with the same pathological tumour size and nodal status at diagnosis. So, because deprived women were less likely to be treated at a regional RT centre they appear to be offered fewer treatment options.

Surgical treatment provides a good example. For women diagnosed in 1998, the prevalence of mastectomy (48%) and breast-conserving surgery (36%) was similar to that seen in 1997, and the treatment differences between the deprivation groups remained (45% of affluent compared to 54% of deprived women had a mastectomy; 40% compared to 28% had breast-conserving surgery). So, inequalities in treatment practice evident in 1997 were still prevalent in 1998. Even if these do not impact on survival, they should not exist. Around

90% of breast cancer registrations for 1998 were matched on to the linked database at the time of this analysis (May 2001). The national clinical guidelines on breast cancer (October 1998)¹⁶⁵ produced by the Scottish intercollegiate guidelines network (SIGN) set out the clinical setting for mastectomy and breast-conserving surgery, and we will be able to assess their impact when the 1999 data are available.

Most of the hospitals treating breast cancer patients in Scotland see women from all deprivation groups, but two of the largest hospitals do not. Thus, 17% of affluent women were treated in hospitals that did not treat any of the deprived women, the majority (16% of affluent women) in Aberdeen Royal Infirmary alone. Similarly, 7% of deprived women were treated at hospitals that did not treat any affluent women, and no less than 1 in 5 (21%) of all deprived women were treated in Glasgow Western Infirmary. Differences in treatment practice between hospitals can thus have a marked effect on the type(s) of treatment received by women in different deprivation groups. Possible recording error in reporting the type of treatment on the hospital discharge records (SMR01s) needs to be considered. Quality assurance exercises have been performed (see Chapter 2) by the ISD Quality Assurance Team on a sample of SMR01 data from 1997 for all hospitals in Scotland. The main operation code was found to be 96% accurate at the three-digit level and the 'other' operation codes were found to be 94% accurate. There were 62 mastectomy or breast-conserving operations in the QA exercise of which the majority (94%) were recorded in the main operation. No differences in recording these specific operations were observed between hospitals, so the differences in treatment options observed are real field (Fiona MacKenzie, ISD Quality Assurance Team, personal communication).

These data support previous findings: differences in ER status and treatment options varied between affluent and deprived women, but these differences were not strong enough to completely account for survival differences in these data; a Scottish audit of patients diagnosed in 1993 gave similar results¹⁵. Deprived women were also more likely to present with metastatic disease, as previously noted in a study of 417 women diagnosed with breast cancer in Glasgow during 1992-93¹⁴³. An earlier study¹⁵³ had noted that older women and those living in more deprived areas were less likely to be treated in a regional RT centre. The analysis presented here show this was still the case for women diagnosed in 1997, and there has been a recent demand for managed clinical networks and teleconferencing, as opposed to a small number of cancer centres treating all the cases¹⁵².

It has previously been noted that tumour stage, ER status and grade are not independent prognostic factors. Grade 3 tumours are more likely to be ER negative¹⁵⁴ and large tumours are more likely to be node positive¹⁵⁶. The data presented here support these findings; 48% of women with grade 3 tumours were ER-negative, compared to 8% with grade 1, 15% with grade 2 and 26% with unknown grade. The tumour was node negative for 68% of women with small (pT1) tumours, 42% of women with pT2 tumours and 26% of women with pT3 tumours.

There was evidence of a lower than expected proportion of lobular carcinomas for deprived women, although survival did not vary by histological type. As this has not been noted before, to my knowledge, I investigated it further with datasets of women diagnosed with breast cancer in Scotland during 1986-90 and 1991-95, and England and Wales during 1986-90. Two of the English registries had a very high proportion of unspecified (80003 or 80103) morphology codes and were excluded, however, for all the other datasets the proportion of lobular carcinomas was lower in the deprived group than expected, although not always significantly so. In Scotland, the proportion of deprived women with lobular carcinomas was 5.7% compared to 6.5% in affluent women in 1986-90 ($p=0.192$), and 6.5% compared to 7.8% in 1991-95 ($p=0.014$). For England and Wales as a whole the proportions were 5.6% in deprived compared to 7.3% in affluent women ($p<0.001$). If we consider one large Scottish hospital, Glasgow Western Infirmary, for patients diagnosed during 1997, the same results are evident. This does suggest that, in addition to ER status, the distribution of tumour type may also vary by deprivation group.

A further point to note is that both clinical and pathological tumour size and nodal status were retained in the final survival model, indicating that both measures were independently predictive of survival. Within each pathological tumour stage, survival varied significantly by the clinical tumour stages grouped therein. Overall, 43% of women were assigned to a different clinical and pathological size group and 38% to different clinical and pathological nodal status groups (including unknown vs. known). These findings strongly support the view that the two types of measure should not be combined into a single variable.

The validity of the imputed data hinges on whether the missing data were missing at random, which is particularly uncertain given the bias of missing values towards the deprived groups. Tumours for which size, nodal status and ER status were unknown were treated as

separate categories in the analyses. Imputation was only carried out for grade, metastatic status and treatment intent. It should be safe to assume that all women receiving treatment with curative intent or who were screen-detected did not have metastatic disease; applying this assumption meant that the final imputation was required for only 12% of the women. Grade, however, was based on imputation of almost a third of the dataset. Checks of survival differences between categories when using imputed data produced estimates similar to those expected from the literature. The main findings of the analysis are not influenced by the method of analysing the unknowns.

Significant deprivation-specific differences in survival obtained from a model including treatment intent (palliative, curative or unknown; Table 5.9, model 4a) became smaller (and non-significant) when the treatment intent was imputed (Table 5.9, model 4b). Treatment intent is difficult to interpret as it is a very "soft" variable; it is not often stated explicitly in the medical notes and the cancer registration officers may use their own judgement in recording it. The information used for the imputation of treatment intent was type of surgery, metastatic status, grade and age. If women were incorrectly assigned by the imputation process (based on metastatic status, grade, type of surgery and age), then the difference in estimates for model 4a and 4b would have been influenced by metastatic status and grade, because type of surgery and age were included in models 4a and 4b in their own right. Interestingly, a model containing type of surgery, chemotherapy, hormone therapy, imputed metastatic status and imputed grade appears to account for most differences in survival between affluent and deprived women ($RR=1.11$; $p=0.421$).

Overall, differences in tumour characteristics appear to be the most important at explaining the differences in survival between affluent and deprived women, and the results of this chapter confirm that deprived women are still more likely to present with ER-negative tumours and with metastatic disease. These are women diagnosed at a time when everyone should be well aware of breast cancer due to huge publicity it has had over recent years. However, some women are still not presenting with early breast symptoms. Survival will never be truly equitable across Scotland until we succeed in encouraging these women to come forward before their disease is advanced.

The widely varying treatment offered to women with breast cancer across Scotland also appears to be important. The treatment options available to women with breast cancer

seem to relate to the hospital they attend and the consultant who sees them. To a certain extent, treatment differences will be 'appropriate' when they are due to the different stage of disease and general health of the patients, but within groups of women with similar tumour characteristics (e.g. tumour pathological size) substantial differences still remain, and this seems unacceptable.

It would be interesting to prolong the follow-up of the patients studied here; 2 years is a very short follow-up interval for breast cancer, where survival is relatively good. From previous work, however, it is not likely that deprivation-specific differences in survival observed at 2 years will reduce with time since diagnosis¹⁶⁶. Similar data for women diagnosed during 1998 will be available shortly, and it would be worthwhile to repeat the analyses for these patients. We will be able to use routine data to assess whether hospitals are complying with the SIGN guidelines introduced in 1998, and whether changes in treatment practice have been made. In particular, the type of operation and workload of hospitals performing the operations can be monitored. A prospective breast cancer audit, which has recently been set up in Scotland, should answer these questions in the future.

In conclusion, the results of this chapter indicate that differences in tumour characteristics and treatment options are responsible for between half and two-thirds of the survival variations observed between affluent and deprived women diagnosed with breast cancer in Scotland during 1997. The data on treatment are crude, and data on tumour characteristics were missing for a substantial minority of patients, so the effects seen are likely to be even larger in reality. These differences in survival are largely avoidable. They could be reduced by carefully targeted awareness campaigns aimed at deprived women and more rigorous adherence by clinicians to SIGN guidelines on how to treat breast cancer. Even if they had no impact on survival, differences in treatment of the kind seen here should not exist in an equitable health service.

COLORECTAL CANCER

Background

Colorectal cancer encompasses all tumours of the colon, recto-sigmoid junction, rectum and anus (ICD10 C18-C21). With the exception of the international comparisons in the background section, the analyses in this chapter are restricted to colon (C18) and rectal (C20) cancers, jointly referred to as colorectal cancer where applicable. Recto-sigmoid junction (C19; 8% of large bowel cancers) and anal (C21; 2%) cancers are excluded due to small numbers, because oncologists treat anal cancers differently, and because there is some argument about the classification of recto-sigmoid cancers.

Colorectal cancer is the third most common cancer in males (14.5% of all cancers) and females (13.1%) in Scotland. Cancer of the colon constitutes about two thirds of cases of colorectal malignancy, with 2 139 patients diagnosed with colon and 884 with rectal cancer in Scotland in 1997. For both colon and rectal cancers incidence is higher in males, and male incidence has been increasing, particularly for rectal cancer, widening the gap in incidence between males and females. Incidence in females remained stable over the 18-year period examined (Figure 6.1).

Incidence of both colon and rectal cancer increases with increasing age, and although incidence is higher in men overall, it is actually higher in women at older ages (Figure 6.2), particularly for colon cancer patients. This is not reflected in the overall (age-standardised) rates, which give more weight to the younger age groups. Mortality from colon cancer is decreasing slightly for both males and females, but there is no similar trend for rectal cancer, for which mortality rates have been stable over the 20-year period shown (Figure 6.1). In 1999, 1 456 patients died of colorectal cancer in Scotland, making it the second most common cause of cancer-related death in Scotland after lung cancer.

Figure 6.1: Colorectal cancer in Scotland: trends in incidence (1979-97) and mortality (1979-99), all ages (European age-standardised rates)

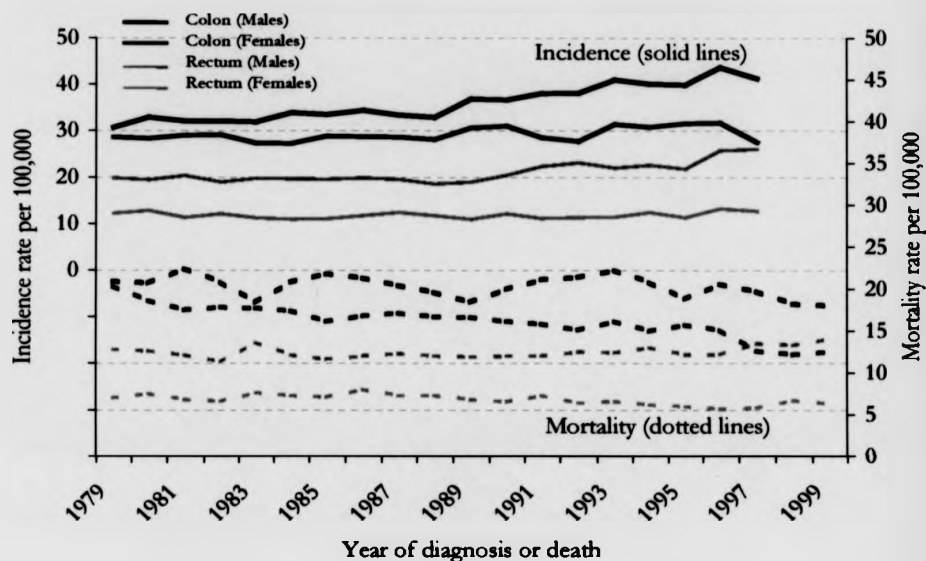
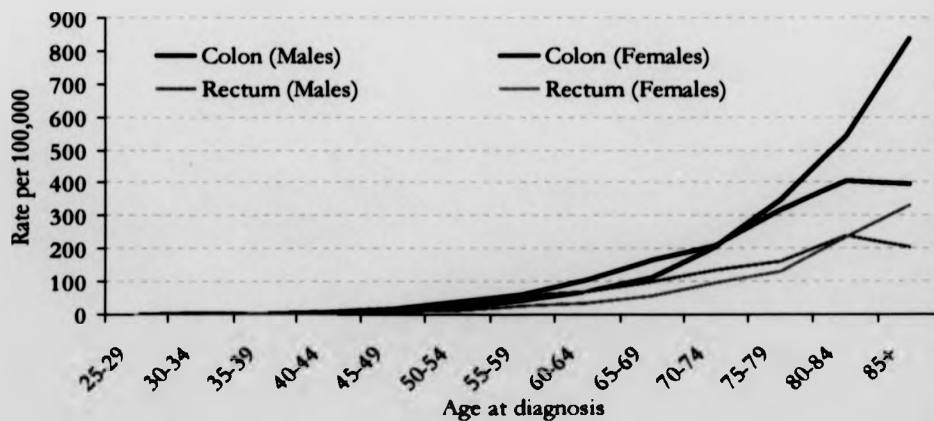
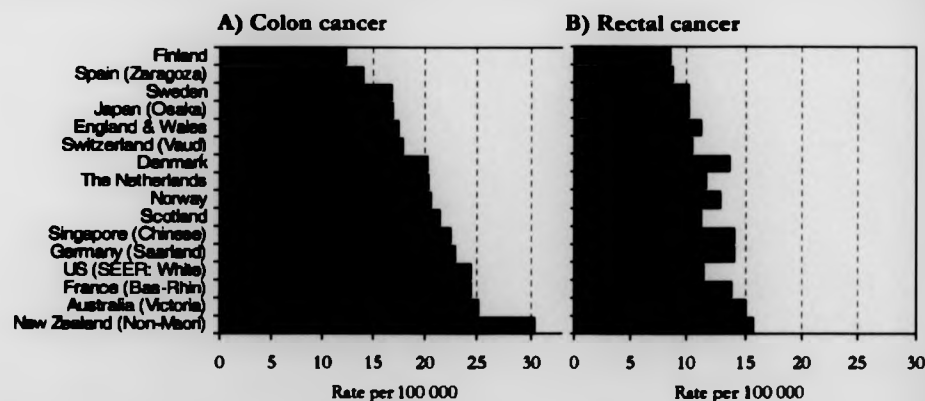


Figure 6.2: Age-specific incidence of colorectal cancer in Scotland for patients diagnosed in 1997, by sex



Incidence of colon cancer is higher in Scotland than in most other European countries but lower than in the USA, Australia and New Zealand. Incidence of rectal cancer is similar to the average for Europe and the USA (Figure 6.3). Substantial differences in incidence between health boards within Scotland also exist, with comparatively low incidence in Lanarkshire and Forth Valley and high incidence in Grampian and Greater Glasgow¹⁶⁹. It is estimated that around two thirds of colorectal cancers can be accounted for solely by the environment and the remaining third by genetic susceptibility¹⁷⁰. Known inherited predisposition genes include hereditary bowel cancer which accounts for around 5% of cases (comprising the very rare familial adenomatous polyposis (FAP) and the more common hereditary non-polyposis colorectal cancer (HNPCC))¹⁷¹.

Figure 6.3: International comparison of colorectal¹ cancer incidence, around 1988-92² (world age-standardised rates)



Source: Cancer Incidence in Five Continents, Volume VII¹⁶⁸

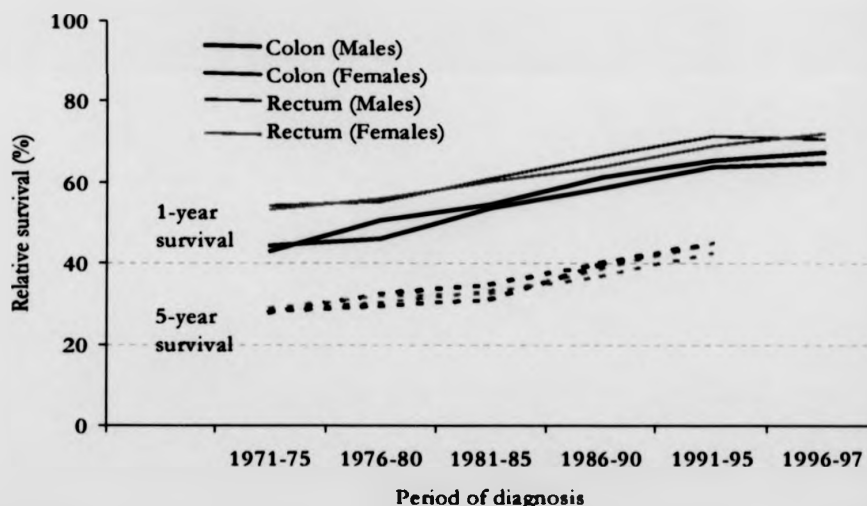
¹ Defined here as ICD10 C18-C21

² The Netherlands data includes the period 1989-92, England and Wales includes 1988-90, Spain includes 1986-90 and Finland includes 1987-92

Over the next decade the incidence rate of colorectal cancer in Scotland is not expected to change, but since 45% of patients are aged over 75 at diagnosis and the population in Scotland is ageing, the annual number of new cases is expected to increase by around 16%¹⁵², and substantially more if screening is introduced. These cancers will, therefore, be of continuing public health importance.

Due to the somewhat vague symptoms of colorectal cancer, and because some patients may not appreciate the significance of more definite symptoms, such as rectal bleeding¹⁷², the majority of cases are not diagnosed until the disease has spread beyond the bowel. Consequently, around three in five patients die as a direct result of the disease within five years of diagnosis. Survival has, however, improved significantly for patients diagnosed over the 27-year period from 1971-97. For colon cancer patients, one-year survival increased from 44% to 66% and five year survival increased from 28% to 45%, and for rectal cancer patients, one-year survival increased from 54% to 71% and five-year survival from 28% to 44% (Figure 6.4).

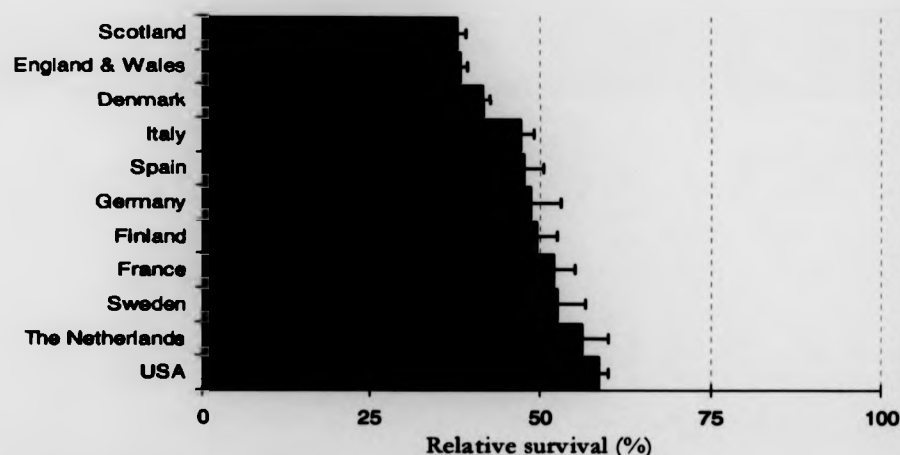
Figure 6.4: Patients diagnosed with colorectal cancer in Scotland during 1971-97: trends in relative survival by sex



Survival is most favourable in young females, and decreases with increasing age in both sexes. Most of the higher mortality in elderly patients is seen in the first year following diagnosis, so may be related to mode of presentation and stage of disease at diagnosis¹. By around six years after diagnosis, patients with colon cancer have a similar survival to the general population. Rectal cancer patients continue to die from the cancer even 10 years after diagnosis.

Despite recent improvements over time, survival is still significantly worse in Scotland than in other European countries and particularly the USA (Figure 6.5). Some studies¹⁷³ indicate that international differences in survival are related mainly to stage at diagnosis, which is generally more advanced in countries with poor survival. However, not all of the international variability can be accounted for by stage at diagnosis, and it has been hypothesised that some of the remaining variation may be explained by differences in management of the disease¹⁷⁴. The validity of these international comparisons are questioned elsewhere¹⁷⁵.

Figure 6.5: Colorectal¹ cancer: international comparison of five-year relative survival (with 95% confidence intervals), selected countries², diagnosed around 1985-89, all ages



Sources: Berrino *et al.*⁴, Gatta *et al.*¹³⁹, Coleman *et al.*⁴

¹ Defined here as ICD10 C18-C21

² Patients aged 15-99 for Scotland; patients diagnosed 1986-90 and aged 15-99 for England & Wales

In this chapter, the survival of 3 009 patients (3 023 cancers; 14 patients had a cancer at both sub-sites during 1997) diagnosed with colorectal cancer in Scotland in 1997 is investigated to identify reasons for differences in survival by deprivation category. For definitions of the variables included in the analyses, please refer to Chapter 2.

Results and commentary

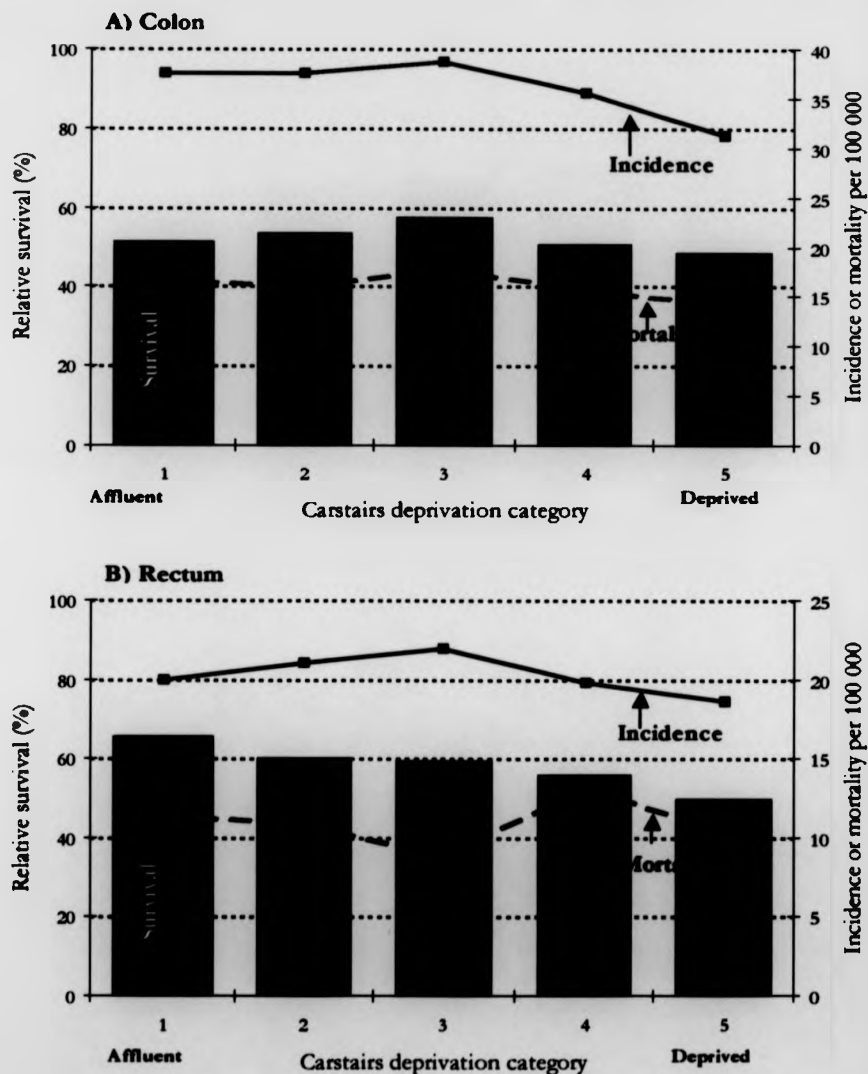
The incidence rate of colon cancer was 8% higher in people from the most affluent areas (herein referred to as affluent patients or the affluent group) compared to people from the most deprived areas (deprived patients or the deprived group) in Scotland in 1997 (Figure 6.6). There was little variation in mortality across the deprivation groups. Survival two years after diagnosis was slightly higher in the affluent than the deprived group (51% compared to 48%) although there was no trend across the deprivation groups, indicating that differences in survival between deprivation groups seen in the earlier periods (see Chapter 3) have diminished.

The incidence rate of rectal cancer was also higher for people living in affluent compared to deprived areas, although there was no clear trend across the deprivation groups. There was also little variation in mortality across the deprivation groups, however, survival two years after diagnosis was significantly higher in the affluent than the deprived group (61% compared to 49%; Figure 6.6).

Overall, 2 139 patients aged 25 and over were diagnosed with colon cancer in Scotland in 1997, of whom 919 (43%) were from deprivation groups 1 and 2 and 763 (36%) from deprivation groups 4 and 5. There were 884 patients aged 30 and over diagnosed with rectal cancer; 375 (43%) from deprivation groups 1 and 2 and 316 (36%) from deprivation groups 4 and 5 (Table 6.1).

Colon cancer was equally common in males and females (50%); however, rectal cancers were more common in men (60%). These proportions were similar between the deprivation groups. The distribution of age at diagnosis was similar for colon and rectal patients, and across the deprivation groups, with median age of 73 years and inter-quartile range from 64 to 80 years. Colon or rectal cancer was the first primary malignancy for 2 740 (91%) of patients; 20 patients had two cancers diagnosed simultaneously, and these were both within the large bowel for 12 patients; 45 patients had a previous primary at the same site; 204 patients had a previous primary at another site, and these were both within the large bowel and diagnosed in 1997 for 2 patients. For the 14 (12+2) patients who had a diagnosis of both colon and rectal cancer within 1997, only the earliest is considered whenever data for colorectal cancers combined is analysed.

Figure 6.6: Patients diagnosed with colorectal cancer in Scotland in 1997: incidence¹ and two-year relative survival², and mortality¹ in 1999, by deprivation category



¹ Age-standardised rates per 100 000 person-years at risk (European standard population)

² Using deprivation-specific life tables

Table 6.1: Patients diagnosed with colorectal cancer in Scotland during 1997: demographic data by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	No. of females	Median age (inter-quartile range)	Cases for which:				No. of urban residents ⁴	
				First primary	Simultaneous primary ²	Previous primary at same site	Previous primary elsewhere ³		
Colon									
Affluent	455 (21%)	222 (49%)	74 (65-82)	402 (88%)	3 (1%)	9 (2%)	41 (9%)	187 (41%)	
2	464 (22%)	237 (51%)	74 (65-80)	422 (91%)	4 (1%)	11 (2%)	27 (6%)	85 (18%)	
3	457 (21%)	234 (51%)	73 (65-79)	409 (89%)	6 (1%)	8 (2%)	34 (7%)	132 (29%)	
4	400 (19%)	196 (49%)	73 (63-80)	369 (92%)	2 (1%)	7 (2%)	22 (6%)	181 (45%)	
Deprived	363 (17%)	181 (50%)	73 (66-80)	328 (90%)	3 (1%)	8 (2%)	24 (7%)	298 (82%)	
Total	2,139 (100%)	1,070 (50%)	74 (65-81)	1,930 (90%)	18 (1%)	43 (2%)	148 (7%)	883 (41%)	
Rectum									
Affluent	176 (20%)	75 (43%)	71 (63-79)	163 (93%)	2 (1%)	0 (0%)	11 (6%)	79 (45%)	
2	199 (23%)	71 (36%)	71 (60-79)	184 (92%)	4 (2%)	0 (0%)	11 (6%)	46 (23%)	
3	193 (22%)	78 (40%)	72 (63-79)	176 (91%)	5 (3%)	0 (0%)	12 (6%)	53 (27%)	
4	164 (19%)	66 (40%)	72 (64-80)	147 (90%)	2 (1%)	1 (1%)	14 (9%)	79 (48%)	
Deprived	152 (17%)	60 (39%)	72 (64-78)	140 (92%)	1 (1%)	1 (1%)	10 (7%)	121 (80%)	
Total	884 (100%)	350 (40%)	72 (63-79)	810 (92%)	14 (2%)	2 (0%)	58 (7%)	378 (43%)	
Colorectal total ¹	3,009 (100%)	1,415 (47%)	73 (64-80)	2,740 (91%)	20 (1%)	45 (1%)	204 (7%)	1,257 (42%)	

¹ 14 patients are in both analysis groups and are only included once (earliest diagnosis) in these totals

² For 12 of these 20 patients, the simultaneous primary was also in the colon or rectum (20 patients, 32 colorectal primaries in 1997)

³ 2 of these patients had a previous primary in the other sub-group (colon or rectum) in 1997 (204 patients, 206 colorectal primaries in 1997)

⁴ Chi-square test for association between deprivation and urban dwelling: $p < 0.001$ for colon and rectal cancer patients

The patients with a previous primary at the same site are included in the analyses, as this fact could help explain the differences in survival being investigated.

The breakdown of deprivation group by health board and rurality was similar to that seen for breast cancer (see Chapter 5). Overall, 42% of patients came from urban areas, but due to variations in the affluent and deprived population mix in urban and rural areas, this varied considerably between deprivation groups, with 81% of deprived patients being urban residents compared to 42% of affluent patients (Table 6.1).

Organisation of services

The Calman-Hine report¹⁰¹, published in 1995, recommended increased specialisation amongst those treating patients with colorectal cancer in England and Wales, and the adoption of a truly multi-disciplinary approach to its management as being central to improved standards of care. Centralisation of the surgical management of colorectal cancer and the formation of a sufficient critical mass of specialist surgeons in such centres to allow 24-hour emergency cover for colorectal emergencies was also the aim of the former Scottish Cancer Coordinating and Advisory Committee (SCCAC)¹⁰². The increasing use of pre-operative radiotherapy will necessarily lead to centralisation of care, as only large cancer centres can offer the necessary facilities.

Of the patients diagnosed with colorectal cancer in 1997, 50% of those aged under 75 attended one of the regional radiotherapy (RT) centres; for those aged 75 and over this figure was 34%. The likelihood of attending a regional RT centre varied significantly by deprivation category. For colon cancer, 52% of affluent compared to 36% of deprived patients attended a regional RT centre; for rectal cancer, 64% of affluent compared to 49% of deprived patients attended a regional RT centre (Table 6.2). Affluent patients were also significantly more likely than patients from other deprivation groups to receive their main treatment at a regional RT centre.

Around 33% of patients (31% colon and 37% rectal) were diagnosed in a low-workload hospital. For colon cancer there was no clear gradient across the deprivation groups. For rectal cancer, however, affluent patients were actually more likely to be diagnosed in a low-workload hospital (34% compared to 18% of deprived patients). In contrast, a study in

south-east England found that colorectal cancer patients from the lower social classes were more likely to be admitted to hospitals with a small workload¹⁴⁹.

For patients diagnosed with colorectal cancer in Scotland in 1997, 42% of patients had their main treatment (defined as the hospital of surgery, or for non-surgical patients the hospital of first 'other' treatment) in a high-workload hospital, 27% in a medium-high workload hospital, 20% in a medium-low workload hospital, and 10% in a low-workload hospital. For colon cancer there was no clear gradient across the deprivation groups. For rectal cancer, affluent patients were more likely to be treated in a high-workload hospital (53% compared to 39% of patients in the other deprivation groups; $p < 0.001$). There is some evidence linking workload and outcome for colorectal cancer³¹, in particular for the surgery of rectal cancer¹⁷⁶. However, workload was not found to be related to outcome in a study of patients in the north-west England¹⁷⁷ or in an audit of Yorkshire patients¹⁷⁸, once case-mix and treatment factors were taken into account. The authors of the Yorkshire audit concluded that the importance of workload is difficult to measure, as it is not independent of treatment decisions or specialisation. In a study from Northern Ireland of patients diagnosed in the early 1990s, no surgeon effect was demonstrated and outcome was actually worse for patients treated at higher workload compared to low workload hospitals¹⁷⁹.

The specialty of the surgeon has been shown to be an important prognostic indicator in studies in Glasgow²⁸ and south-east Scotland¹⁸⁰. For patients diagnosed in Scotland in 1997, it was not possible to identify the operating surgeon from the routine data; however, the clinician responsible for the patient at the time of surgery could be identified. Of the 1 787 colon cancer patients receiving surgery, 24% were managed by a high-workload clinician (at least 30 cases per year), 39% by a medium-workload clinician (20-29 cases) and 30% by a low-workload clinician (<20 cases). For the 711 rectal cancer patients receiving surgery, 21% were managed by a high-workload clinician, 32% by a medium-workload clinician, and 39% by a low-workload clinician. For those not treated surgically, 49% of colon and 45% of rectal cancer patients were seen only by a low-workload clinician in the three-month period after diagnosis. Affluent patients with rectal cancer were more likely to be seen by a high-workload clinician than rectal cancer patients in the other deprivation groups (36% compared to 23%; $p = 0.023$). Most patients (83% of colon and 88% of rectal) were seen in a specialist department within 3 months of their cancer diagnosis, and this proportion did not vary by deprivation group (Table 6.2).

Table 6.2: Patients diagnosed with colorectal cancer in Scotland during 1997: access to health care by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Attended a regional RT centre ¹	Attended a specialist department ²	Main treatment at a regional RT centre ³	Treated in a high-workload hospital ⁴	Seen by a high-workload clinician ⁵	Emergency admission	More than two weeks' delay between diagnosis and treatment ⁶	All of care in one hospital
Colon									
Affluent	455	238 (52%)	373 (82%)	191 (42%)	236 (52%)	126 (31%)	172 (38%)	208 (54%)	66 (15%)
2	464	190 (41%)	384 (83%)	113 (24%)	159 (34%)	114 (27%)	171 (37%)	217 (53%)	50 (11%)
3	457	189 (41%)	381 (83%)	133 (29%)	199 (44%)	124 (29%)	184 (40%)	216 (54%)	52 (11%)
4	400	110 (28%)	336 (84%)	57 (14%)	142 (36%)	102 (27%)	153 (38%)	166 (50%)	60 (15%)
Deprived	363	132 (36%)	297 (82%)	97 (27%)	166 (46%)	97 (28%)	153 (42%)	159 (53%)	52 (14%)
Total	2,139	859 (40%)	1,771 (83%)	591 (28%)	902 (42%)	563 (28%)	833 (39%)	966 (53%)	280 (13%)
Significance ⁷		$p<0.001$	$p=0.843$	$p<0.001$	$p<0.001$	$p=0.339$	$p=0.415$	$p=0.258$	$p=0.216$
Rectum									
Affluent	176	112 (64%)	155 (88%)	79 (45%)	93 (53%)	57 (36%)	27 (15%)	123 (77%)	22 (13%)
2	199	90 (45%)	168 (84%)	56 (28%)	72 (36%)	46 (25%)	29 (15%)	134 (75%)	23 (12%)
3	193	98 (51%)	176 (91%)	57 (30%)	82 (42%)	35 (20%)	29 (15%)	129 (75%)	20 (10%)
4	164	76 (46%)	139 (85%)	28 (17%)	59 (36%)	38 (26%)	29 (18%)	111 (80%)	25 (15%)
Deprived	152	74 (49%)	138 (91%)	41 (27%)	60 (39%)	33 (23%)	24 (16%)	93 (75%)	26 (17%)
Total	884	450 (51%)	776 (88%)	261 (30%)	366 (41%)	209 (26%)	138 (16%)	590 (76%)	116 (13%)
Significance ⁷		$p=0.009$	$p=0.399$	$p<0.001$	$p=0.007$	$p=0.023$	$p=0.250$	$p=0.195$	$p=0.518$

¹ At some point during the cancer spell

² Within 3 months of diagnosis

³ Number of patients where main treatment was performed at a regional RT centre (hospital of surgery, or hospital where the first non-surgical treatment was received for non-surgical patients)

⁴ Hospital seeing at least 30 colon or 20 rectal cancer patients (see Chapter 2 for details of the workload groupings)

⁵ Clinician seeing at least 20 colon or 20 rectal cancer patients (see Chapter 2 for details of the workload groupings); percentage of those with clinician details

⁶ Days between diagnosis and definitive treatment; percentage of those with a definitive treatment date

⁷ Chi-square test for association

Delay

Most patients developing colorectal cancer will eventually present with symptoms. Primary symptoms include abdominal pain, persistent rectal bleeding without anal symptoms, and change in bowel habit. Secondary effects include severe iron deficiency anaemia, intestinal obstruction including abdominal mass or rectal mass, weight loss and nausea. A large proportion of colorectal cancer patients have previously been diagnosed with irritable bowel disease.

Among patients diagnosed in Scotland in 1997, 32% of patients presented initially as an emergency (39% of colon and 16% of rectal cancer patients). This is similar to England, where one in three colon and one in ten rectal cancer patients are reported to present as an emergency¹⁸¹. For colorectal cancer patients diagnosed in Glasgow in the 1980s, 36% presented as an emergency and had a poorer outcome than patients with an elective admission, even after accounting for tumour stage¹⁸².

For patients diagnosed in 1997, those from all deprivation groups were equally likely to present as an emergency (Table 6.2). This contrasts with a study of patients diagnosed in south-east England during 1992-95 where deprived patients were more likely to present as an emergency¹⁴⁹. For patients diagnosed in Scotland in 1997, emergency admission was strongly related to age and tumour stage. Of patients aged 80 and over, 39% presented initially as an emergency compared to 29% of younger patients. Of patients with Dukes' D tumours, 39% presented initially as an emergency compared to only 12% of patients with Dukes' A, and 32% with Dukes' B and C tumours.

Most patients presenting as emergencies are likely to benefit from resuscitation and stabilisation, with subsequent appraisal and operation by an appropriately trained surgeon and team. Few require early surgery. There is no definitive evidence that earlier referral in itself will change the stage of colorectal cancer at diagnosis, as it is probable that colorectal cancers are slow growing and may be present in the bowel for several years before diagnosed. The main probable benefit of earlier diagnosis is that it may allow disease management to be planned, thus avoiding emergency surgery which has a high post-operative mortality^{182,183}.

For over half (53%) of colon and three-quarters (76%) of rectal cancer patients diagnosed in Scotland in 1997, at least two weeks elapsed between diagnosis and the definitive treatment. This is unlikely to greatly affect survival but may increase the patient's anxiety. There was no clear gradient across the deprivation groups. There are three other main sources of delay in a cancer patient's journey: patient delay, GP delay in referral, and delays in diagnosis. Together they can amount to a substantial length of time. It has been estimated that almost half of patients delay many weeks before consulting their GP¹⁸⁴. There are guidelines for GPs on identifying patients with suspected colorectal cancer for urgent referral¹⁰³ but each GP in the UK will on average only see one new case of colorectal cancer each year¹⁸⁵, so delays will occur. Once the patient has been referred to hospital for investigation, it is estimated a third of patients wait more than one month from first hospital consultation to diagnosis¹⁸⁶. This is estimated from a small (N=59) sample of colorectal cancer patients in an audit conducted at an Edinburgh teaching hospital. These sources of delay cannot be examined with the routine data available for this thesis.

Most patients (87%) attended more than one hospital during their cancer spell, which could be indicative of the patient having access to multidisciplinary teams. Deprived patients with rectal cancer were slightly less likely to transfer between hospitals (83% compared to 87% of affluent patients; not significant; Table 6.2).

Mode of presentation

When a patient presents with a suspected colorectal cancer they will usually receive a flexible colonoscopy followed by endoscopic removal of benign adenomatous polyps, or barium enema followed by other imaging procedure (ultrasound, conventional CT or MRI). Patients investigated by sigmoidoscopy (usually flexible), or patients whose colon was not visualised adequately at colonoscopy are generally investigated by double contrast barium enema (DCBE). Computerised tomographic (CT) colonography, which uses 3D imaging, was not used for patients diagnosed during 1997.

Survival is primarily determined by pathological tumour stage at presentation, and Dukes' stage is recorded on SOCRATES (see Chapter 2). This measures the extent of bowel wall invasion, nodal status and the presence of metastases. For patients diagnosed in Scotland in 1997, the proportion of staged tumours within each stage for colon cancer patients was 9% with Dukes' A, 40% with Dukes' B, 33% with Dukes' C and 18% with Dukes' D tumours.

The corresponding proportions for rectal cancer patients were 23%, 32%, 29% and 16%, respectively (Table 6.3). These distributions are more favourable than that seen in Scotland in 1993, where 10% of colorectal cancers were Dukes' A, 39% were Dukes' B, 27% were Dukes' C and 25% were Dukes' D tumours¹⁸⁷, and is also more favourable than reported in published data from other audits in the UK from the early 1990s^{180,188,189}, indicating that patients are now being diagnosed earlier. Even given this improvement over time, however, almost half the tumours have still metastasised to the lymph nodes or beyond when diagnosed.

For patients diagnosed with colorectal cancer in Scotland in 1997, 15% did not have stage recorded. These were more likely to be older patients (28% of patients aged 80+ had stage missing compared to 11% of younger patients; $p < 0.001$), affluent patients (19% compared to 12% of deprived patients), those not receiving surgery (61% compared to 7% of patients who did receive surgery), those treated with palliative intent (24% compared to 4% treated with curative intent, and 28% of those whose treatment intent was unknown), patients with serious comorbidity and patients seen by a low-workload clinician. Patients admitted as an emergency and patients not seen in a specialist department were also more likely to have missing stage information; however, this seemed to be a result of these patients being more likely to be seen by a low-workload clinician.

Of those patients with known stage, the distribution was similar across deprivation groups for colon cancer patients. However for rectal cancer, deprived patients were more likely to present with Dukes' D disease (21% compared to 10% of affluent patients) although there was no clear trend in the stage distribution across the deprivation groups. The proportion of patients with no stage recorded (15%) was similar to that seen in an audit of colorectal cancer patients diagnosed in Scotland in 1993 (13%)¹⁸⁷. In that audit the proportion with missing stage did not vary between deprivation groups and the investigators found that the stage distribution was similar between affluent and deprived patients; however they presented data for colon and rectal cancer patients combined, which may mask differences in stage at presentation at the two sites.

Table 6.3: Patients diagnosed with colorectal cancer in Scotland during 1997: clinical stage and grade by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Dukes stage ¹						Grade ¹				
		A	B	C	D	Unknown		1	2	3/4	Unknown	
Colon												
Affluent	455	31 (8%)	154 (41%)	119 (32%)	70 (19%)	81 (18%)	20 (6%)	240 (71%)	78 (23%)	117 (26%)		
2	464	35 (9%)	147 (37%)	146 (37%)	66 (17%)	70 (15%)	17 (5%)	231 (70%)	83 (25%)	133 (29%)		
3	457	32 (8%)	175 (43%)	132 (32%)	69 (17%)	49 (11%)	26 (7%)	249 (70%)	82 (23%)	100 (22%)		
4	400	33 (9%)	136 (39%)	103 (30%)	77 (22%)	51 (13%)	11 (4%)	226 (75%)	65 (22%)	98 (25%)		
Deprived	363	30 (10%)	117 (37%)	109 (35%)	58 (18%)	49 (13%)	13 (4%)	215 (74%)	62 (21%)	73 (20%)		
Total	2,139	161 (9%)	729 (40%)	609 (33%)	340 (18%)	300 (14%)	87 (5%)	1,161 (72%)	370 (23%)	521 (24%)		
Significance					$p=0.4202^2$	$p=0.032^1$			$p=0.535^2$	$p=0.037^1$		
Rectum												
Affluent	176	38 (27%)	39 (28%)	50 (35%)	14 (10%)	35 (20%)	8 (6%)	102 (73%)	30 (21%)	36 (20%)		
2	199	39 (24%)	50 (31%)	42 (26%)	31 (19%)	37 (19%)	7 (5%)	121 (79%)	25 (16%)	46 (23%)		
3	193	41 (26%)	51 (32%)	47 (30%)	20 (13%)	34 (18%)	5 (3%)	125 (78%)	30 (19%)	33 (17%)		
4	164	23 (17%)	55 (41%)	35 (26%)	22 (16%)	29 (18%)	7 (5%)	107 (79%)	21 (16%)	29 (18%)		
Deprived	152	28 (21%)	39 (29%)	40 (29%)	29 (21%)	16 (11%)	5 (4%)	90 (76%)	24 (20%)	33 (22%)		
Total	884	169 (23%)	234 (32%)	214 (29%)	116 (16%)	151 (17%)	32 (5%)	545 (77%)	130 (18%)	177 (20%)		
Significance					$p=0.274^2$	$p=0.200^1$			$p=0.884^2$	$p=0.546^1$		

¹ Percentage of patients with a known category, except 'unknown', presented as a percentage of the total

² Significance of association (Chi-square test) between deprivation category and percentage of patients in each category excluding those in the unknown category

³ Significance of proportion unknown across the deprivation categories (Chi-square test for association)

Grade is another important prognostic indicator for colorectal cancer. Of patients diagnosed in Scotland in 1997 with known grade, the proportion of patients presenting with well-differentiated (grade 1) tumours was very low (5%), compared to 74% presenting with moderately-differentiated and 21% with poorly-differentiated or undifferentiated tumours. These proportions were similar for colon and rectal cancer patients, and across the deprivation groups (Table 6.3). Grade was unknown for 23% of patients, and for colon cancer, affluent patients were more likely to have unknown grade ($p=0.037$). Of patients with missing stage, 69% also had missing grade.

For patients with known stage and grade there was also a relationship, with well-differentiated tumours being predominantly early stage (Dukes' A or B). For colon cancer, 81% of patients with well-differentiated tumours were early stage, compared to 54% of patients with moderately-differentiated and 31% with poorly-differentiated or undifferentiated tumours. For rectal cancer, around half of patients with well- and moderately-differentiated tumours were early stage compared to 28% of patients with poorly-differentiated or undifferentiated tumours.

Diagnosis was microscopically verified for most (92%) patients, with no significant difference between the deprivation groups (Table 6.4). The majority of tumours were adenocarcinomas (79% of colon and 90% of rectal cancers), with some mucinous tumours (8% of colon and 4% of rectal) and the rest being other or unspecific cell types. The proportion of each tumour type was similar across the deprivation groups. The specific cancer location (4th digit of the ICD code) was recorded for colon cancer patients (data not shown), with the most common locations being the sigmoid colon (29%) and caecum (22%). The location was significantly more likely to be unspecified for deprived patients (31% versus 13% of affluent patients; 18% overall), however for patients with known site there were no differences between the deprivation groups.

Screening

Screening is potentially important for colorectal cancer because symptoms do not usually become evident until the tumour is advanced, whereas most cancers result from malignant change in benign adenomatous polyps or villous adenomas that have developed in the lining of the bowel¹⁹⁰. Larger polyps have a greater risk of becoming malignant than smaller ones, and the vast majority (90%) can be removed at colonoscopy¹⁹¹.

Three randomised controlled trials of faecal occult blood test (FOBT) have shown a reduced risk of death for people offered FOBT screening. An overview of these¹⁹² predicts a reduction in mortality of up to 23% in those screened (16% for the whole population invited for screening). A pilot of FOBT colorectal cancer screening is currently underway in part of Scotland for patients aged 50-69 years, and will be completed in 2002. If the pilot is successful and screening is started on a national scale, then it has been estimated that the maximum reduction in mortality for all ages combined will be 8%¹⁵². This is due to lower compliance in the population setting, the accuracy of the FOB test and the restricted age range of those who would be invited.

The sensitivity of FOBT is relatively low – a third to half of cancers will be missed on each round of screening. Flexible sigmoidoscopy can detect 80% of colorectal cancers, and a multi-centre trial investigating this as a strategy for population screening is currently in progress.

There were no screening trials underway in Scotland in 1997, so population screening is not considered in the interpretation of the analyses in this chapter.

Comorbidity

For patients diagnosed in Scotland in 1997, 54% of colon and 29% of rectal cancer patients had comorbidity at diagnosis, as measured by the bed-days score. These percentages were lower when comorbidity was measured by the Scotland or Charlson indices.

Patients from the most deprived areas had greater comorbidity at diagnosis than affluent patients, as measured by the bed-days comorbidity score (Table 6.4). For colon cancer, 60% of deprived compared to 51% of affluent patients had spent more than 10 days in hospital in the two years prior to their cancer diagnosis. For rectal cancer, 39% of deprived compared to 24% of affluent patients had spent more than 10 days in hospital ($p=0.033$). The gradient between affluent and deprived patients was smaller when measured by the Scotland index, and was reversed for rectal cancer patients when measured by the Charlson index.

Table 6.4: Patients diagnosed with colorectal cancer in Scotland during 1997: microscopic verification, comorbidity and post-operative mortality by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Microscopically verified		Comorbidity			30-day post-operative mortality ⁴				
				Bed-days ¹	Scotland ²	Charlson ³					
Colon											
Affluent	455	400	(88%)	231	(51%)	107	(24%)	58	(13%)	16	(4%)
2	464	425	(92%)	243	(52%)	98	(21%)	64	(14%)	26	(6%)
3	457	419	(92%)	246	(54%)	121	(26%)	72	(16%)	26	(7%)
4	400	361	(90%)	217	(54%)	107	(27%)	63	(16%)	18	(5%)
Deprived	363	324	(89%)	217	(60%)	100	(28%)	66	(18%)	26	(9%)
Total	2,139	1,929	(90%)	1,154	(54%)	533	(25%)	323	(15%)	112	(6%)
Significance ⁵			p=0.177		p=0.121		p=0.152		p=0.235		p=0.176
Rectum											
Affluent	176	172	(98%)	43	(24%)	29	(16%)	29	(16%)	4	(3%)
2	199	191	(96%)	50	(25%)	32	(16%)	23	(12%)	9	(5%)
3	193	183	(95%)	59	(31%)	41	(21%)	26	(13%)	5	(3%)
4	164	154	(94%)	48	(29%)	45	(27%)	25	(15%)	9	(7%)
Deprived	152	147	(97%)	59	(39%)	32	(21%)	19	(13%)	8	(7%)
Total	884	847	(96%)	259	(29%)	179	(20%)	122	(14%)	35	(5%)
Significance ⁵			p=0.420		p=0.033		p=0.058		p=0.659		p=0.292

¹ More than 10 inpatient bed-days in the two years prior to cancer diagnosis

² Any one of certain comorbid conditions recorded in the two years prior to one month after diagnosis (see Chapter 1)

³ Any one of certain comorbid conditions recorded in the five years prior to diagnosis (see Chapter 1)

⁴ Percentage of patients receiving surgery

⁵ Chi-square test for association

Treatment

Stage is an important guide to the clinical management of colorectal cancer. Colorectal guidelines published in 1997 by the Scottish Intercollegiate Guidelines Network (SIGN)¹⁹³ suggest that patients with early disease (Dukes' A or B) should receive curative surgery and may not require any further treatment. Patients with metastases (Dukes' D) may undergo technically similar operations but with palliative rather than curative intent. For those with locally advanced disease, or when there is nodal spread (Dukes' C), adjuvant chemotherapy should be considered. Pre-operative radiotherapy may be considered for fixed or tethered rectal tumours where the objective is to down-stage the disease prior to surgery. Post-operative radiotherapy is recommended for rectal tumours with a high risk of recurrence. Chemotherapy or radiotherapy may also be given as palliation for advanced colon or rectal disease.

Surgical resection is the primary curative modality for colorectal cancer patients, with endoscopic resection representing another approach for the small minority of early malignant polyp-cancers. The proportion of curative operations performed, on average, in a recent audit of west of Scotland hospitals was 68% and palliative resection for 25% of patients¹⁹⁴. In combination with curative surgery, pre-operative adjuvant radiotherapy for early stage rectal cancer can impart around 30% reduction in both local recurrence rate and in mortality¹⁹⁵. Although some centres use radiotherapy for all rectal cancers, most specialist centres only use pre-operative radiotherapy for fixed tumours, tethered tumours or very low lesions just above the anal sphincters. Use of peri-operative radiotherapy has been sporadic until recently.

For patients diagnosed in Scotland in 1997, 84% of colon and 80% of rectal cancer patients received surgery (Table 6.5). The surgery was recorded as curative for 62% of patients, palliative for 32% and unknown for 6% of patients. Radiotherapy was rare for colon cancer patients (5%), where it is only recommended for palliative use. In comparison, over a quarter of rectal cancer patients received radiotherapy (30%) and 100 (11%) received radiotherapy before surgery. Radiotherapy prior to surgery was very rare for emergency admission patients. Chemotherapy was slightly more common for colon (19%) than rectal (17%) cancer patients, and comprised largely of patients with late stage (Dukes' C and D) tumours. Overall, 39% of patients with Dukes' C tumours received chemotherapy, which is lower than might be expected; however, around 25% of patients aged less than 80 years have significant cardiac co-morbidity that precludes chemotherapy¹³². Most primary treatment was received within 6 months of diagnosis. Deprived patients were slightly less likely than affluent patients to receive surgery, radiotherapy or chemotherapy.

Treatment rates declined with increasing age. Surgery was undertaken for only 71% of patients over age 80 compared to 88% aged 60-79 and 95% aged under 60. The corresponding rates for radiotherapy were 5%, 13% and 19%, and for chemotherapy were 1%, 19% and 44%, respectively. No treatment at all was recorded for 27% of patients aged over 80, compared to only 9% of those aged 60-79 and only 3% of those aged under 60. A similar age-related treatment effect was also seen in an audit of Yorkshire patients¹⁷⁸.

Most early stage (Dukes' A and B) colon cancer patients received surgery (95%), either alone (86%) or in combination with chemotherapy and/or radiotherapy (9%). Surgery was also

performed for most early stage rectal cancer patients (93%), and 19% received surgery in combination with chemotherapy and/or radiotherapy. Patients with late stage (Dukes' C and D) tumours were less likely than those with early stage tumours to receive surgery alone as treatment for colon (85% received surgery; 34% in combination) or rectal cancer (81% received surgery; 49% in combination; Table 6.6).

Table 6.5: Patients diagnosed with colorectal cancer in Scotland during 1997: treatment received by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Surgery		Radiotherapy		Chemotherapy	
		Within 6 months	Overall	Within 6 months	Overall	Within 6 months	Overall
Colon							
Affluent	455	363 (80%)	372 (82%)	17 (4%)	23 (5%)	83 (18%)	93 (20%)
2	464	392 (84%)	403 (87%)	15 (3%)	27 (6%)	86 (19%)	93 (20%)
3	457	385 (84%)	390 (85%)	19 (4%)	25 (5%)	73 (16%)	81 (18%)
4	400	323 (81%)	329 (82%)	10 (3%)	17 (4%)	56 (14%)	66 (17%)
Deprived	363	288 (79%)	293 (81%)	9 (2%)	12 (3%)	64 (18%)	69 (19%)
Total	2,139	1,751 (82%)	1,787 (84%)	70 (3%)	104 (5%)	362 (17%)	402 (19%)
Significance ¹		p=0.130	p=0.077	p=0.572	p=0.471	p=0.370	p=0.555
Rectum							
Affluent	176	136 (77%)	142 (81%)	59 (34%)	63 (36%)	33 (19%)	38 (22%)
2	199	166 (83%)	170 (85%)	40 (20%)	50 (25%)	25 (13%)	33 (17%)
3	193	157 (81%)	160 (83%)	52 (27%)	58 (30%)	24 (12%)	29 (15%)
4	164	123 (75%)	126 (77%)	45 (27%)	50 (30%)	23 (14%)	25 (15%)
Deprived	152	108 (71%)	113 (74%)	42 (28%)	42 (28%)	23 (15%)	24 (16%)
Total	884	690 (78%)	711 (80%)	238 (27%)	263 (30%)	128 (14%)	149 (17%)
Significance ¹		p=0.043	p=0.065	p=0.070	p=0.240	p=0.418	p=0.446

¹ Chi-square test for association

For rectal cancer patients there is evidence that combining adjuvant therapy with curative surgery can provide worthwhile improvements in both local control and overall survival. The evidence for benefit of adjuvant chemotherapy is restricted to patients with Dukes' C cancers who undergo curative resection^{196,197}. For rectal cancer patients with Dukes' C cancer diagnosed in Scotland in 1997, almost all (96%) received surgery (curative* for 63%), and 41% received adjuvant chemotherapy. However, chemotherapy for patients with Dukes' C tumours was not equally available to all the deprivation groups (52% of affluent

* Treatment intent is difficult to interpret as it is a very "soft" variable; it is not often stated explicitly in the medical notes and the CROs may use their own judgement in recording it.

patients compared to 32% of deprived patients received chemotherapy). There was not a clear trend in chemotherapy across the deprivation groups.

Table 6.6: Patients diagnosed with colorectal cancer in Scotland during 1997: treatment received by Dukes' stage at diagnosis (number and percentage of cases)

Treatment combination	Dukes stage A and B	Dukes stage C and D	Unstaged
Colon			
Surgery alone	767 (86%)	485 (51%)	83 (28%)
Chemotherapy alone	1 (0%)	27 (3%)	5 (2%)
Radiotherapy alone	0 (0%)	3 (0%)	4 (1%)
Surgery and chemotherapy	43 (5%)	272 (29%)	11 (4%)
Surgery and radiotherapy	28 (3%)	23 (2%)	3 (1%)
Surgery, chemotherapy and radiotherapy	9 (1%)	30 (3%)	2 (1%)
Chemotherapy and radiotherapy	0 (0%)	1 (0%)	0 (0%)
No treatment or unknown combination	42 (5%)	108 (11%)	192 (64%)
Rectum			
Surgery alone	300 (74%)	106 (32%)	36 (24%)
Chemotherapy alone	0 (0%)	4 (1%)	1 (1%)
Radiotherapy alone	3 (1%)	12 (4%)	30 (20%)
Surgery and chemotherapy	6 (1%)	44 (13%)	4 (3%)
Surgery and radiotherapy	60 (15%)	57 (17%)	12 (8%)
Surgery, chemotherapy and radiotherapy	12 (3%)	62 (19%)	4 (3%)
Chemotherapy and radiotherapy	0 (0%)	8 (2%)	2 (1%)
No treatment or unknown combination	22 (5%)	37 (11%)	62 (41%)

Of patients receiving surgery, the intent was recorded as curative for 88% of early stage colon cancer patients, 38% of late stage colon cancer patients, 90% of early stage rectal cancer patients, and 47% of late stage rectal cancer patients. For patients with treatment of known (recorded) intent, there were no differences in the intent (curative or palliative) between the deprivation groups, although treatment intent was less likely to be recorded for affluent patients (8% compared to 3% of deprived patients).

Colon cancer patients were less likely than rectal cancer patients to have surgery at a low-workload hospital, although the definitions of hospital workload differ (see Chapter 2); 28% of colon and 26% of rectal cancer patients had surgery at a regional RT centre, 14% colon and 13% rectal at other high-workload hospitals, 30% colon and 25% rectal at medium-workload hospitals, and 28% colon and 36% rectal at low-workload hospitals.

The national guidelines¹⁹³ recommend that surgery for rectal cancer should be restricted to surgeons with a specialist interest in the procedure, due to the difficulty in achieving complete excision of the tumour (clear histological margins), and because wide variations in the rate of "curative" resection, colostomy formation, local recurrence rate, peri-operative mortality and cancer survival between surgeons have been reported in the UK^{180,189,194}. It is stressed that this may be an effect of workload and/or specialisation, but could also be due to case-mix rather than any intrinsic ability of the surgeon or the hospital in which they work. In one large Canadian study, the effect of surgeon-related variables could only account for 10-30% of observed mortality differences¹⁹⁵. This is supported by studies on the effect of specialisation in Germany and the north west of England¹⁷⁷. For patients diagnosed in Scotland in 1997, affluent patients were more likely than deprived patients to be managed by a high-workload consultant at the time of surgery.

For patients diagnosed in Scotland in 1997, those attending a regional RT centre at some point during their cancer spell were the most likely to have their tumour histologically verified (95%), compared to patients attending high-workload (93%), medium-workload (92%) or low-workload (86%) hospitals. They were also more likely to receive chemotherapy (35% compared to 5% of patients seen elsewhere). This may be because patients most suited to adjuvant therapy were being referred to the regional RT centres.

Post-operative mortality

Risk of peri-operative death has been shown to be higher after emergency admission than routine/elective admission, both in England¹⁸¹ and in Scotland¹⁹⁴. For patients diagnosed in Scotland in 1997, the 30-day post-operative mortality rate was 6% for colon and 5% for rectal cancer patients. Patients who first presented as an emergency had a higher post-operative mortality rate than those presenting electively (10% compared to 4%; 11% for those with unknown type of admission). This is lower than that reported in a study conducted at a Glasgow hospital, where the post-operative mortality rate was 9% for elective and 19% for emergency operations¹⁹⁴. In Trent and Wales audits conducted in the early 1990s, the 30-day post-operative mortality rate was 7.6% (22% for emergency and 6% for elective operations)¹⁸⁹. However, in routine Scottish data it is only possible to identify emergency admissions, not emergency operations.

For the Scottish patients diagnosed in 1997, those from deprived areas had the highest post-operative mortality rate (8% compared to 4% in affluent patients; $p=0.080$), and they had higher post-operative mortality whether they were admitted routinely or as an emergency, although the difference was most marked for emergency admissions (5% post-operative mortality for affluent compared to 14% for deprived patients; $p=0.084$).

The 30-day post-operative mortality rate varied by type of hospital. For patients treated at a regional RT centre it was 4%, compared to 8% for those treated at other high-workload hospitals, 6% at medium-workload hospitals and 6% at low-workload hospitals (not significant). Patients seen by a high-workload clinician within 3 months of diagnosis had the lowest post-operative mortality rates (2%) compared to those seen by a medium-workload clinician (5%) or low-workload clinician (8%; $p=0.016$). Patients who were managed by a medium- or high-workload clinician at the time of their operation also had a slightly lower post-operative mortality rate (5%) than those with a low-workload clinician (7%; not significant).

A small review of in-hospital deaths for colorectal cancer patients in south-east Scotland in the 1990s found that 78 of the 187 deaths were avoidable. In particular, 26 occurred following an anastomotic leak, 17 because surgery was delayed, 12 because there was undue delay in making the initial diagnosis and 14 because developing complications were not recognised¹⁹⁹.

Two-year survival

Univariate analyses

Factors that had an influence on the differences in 2-year survival between deprivation groups were investigated in Cox proportional hazards regression models. In the initial model containing deprivation only, the relative risk of death within two years of diagnosis was substantially raised for deprived compared to affluent patients with rectal cancer (RR 1.75 (95% CI 1.25-2.46); $p<0.01$) but not colon cancer (1.13 (0.93-1.37); $p=0.211$) (Table 6.7).

For colon cancer, adjusting for factors relating to the patient, the tumour, the health care system and treatment increased the relative risk of death between affluent and deprived

patients, and after adjusting for differences in tumour characteristics or treatment factors the deprivation-specific differences were often significant, suggesting that differences in survival for colon cancer patients were being masked in the initial analysis including only deprivation.

For rectal cancer patients, adjustment for factors relating to the patient, the tumour, health care system and treatment did not reduce the relative risk of death between affluent and deprived patients with the exception of the workload of the clinician managing the patient at the time of surgery, which appeared to explain around a third of the difference in risk of death between affluent and deprived patients and rendered the difference non-significant (RR reduced from 1.75 to 1.57 (95% CI 0.98-2.51)).

Patient characteristics

Survival was strongly related to age for colon and rectal cancer patients. Survival at two years was significantly higher ($p < 0.001$) for younger compared to older patients (68% for patients aged < 50 compared to 36% for patients aged 80+ with colon cancer; 72% compared to 36% for rectal cancer patients). However, because age did not vary across the deprivation groups, including age in the model significantly improved the model fit but did not account for differences in survival between affluent and deprived patients. Lower survival for older patients is generally attributed to greater comorbidity and more advanced tumour stage, with the proportion of surgically treated patients declining with increasing age. This is true for the patients diagnosed in Scotland in 1997 and has been observed across Europe for patients diagnosed in 1987²⁰⁰. However, survival does not vary appreciably with age for patients diagnosed with colorectal cancer in the USA, and patterns of surgery do not vary for these patients²⁰¹. The models including deprivation and age are used as the null model for the analyses shown in Table 6.7.

Survival was higher for females than males, particularly at younger ages (aged < 50 ; 2-year survival was 74% for females compared to 66% for males). Females tended to be diagnosed at a later age and had a higher proportion of the elderly (25% of females compared to 19% of males were aged 80+), therefore, the overall survival estimates appeared similar for males and females. Inclusion of sex in the null model improved the model fit (see columns 5 and 10 of Table 6.7) for colon and rectal cancer patients, but did not explain differences in the risk of death between the deprivation groups (the RR increased from 1.13 to 1.21 for colon cancer patients and stayed constant at 1.75 for rectal cancer patients).

A northern Scotland study²⁰² of patients diagnosed during 1995-96 found rural colorectal cancer patients to have a poorer survival because of more advanced disease at diagnosis. They measured rurality as distance from a cancer centre. For patients diagnosed in Scotland in 1997, rurality was measured using the GRO population density scale, because it was not appropriate to measure distance without taking into account accessibility^f. Accessibility is complicated to measure with routine data because road size and directness needs to be taken into account, along with availability of public transport. For patients diagnosed in Scotland in 1997, there were no differences in stage at diagnosis for urban and rural residents measured with the GRO rurality scale, and no differences in survival. There were also no differences in survival by health board of residence or for patients who had a history of cancer. None of these factors improved the fit of the null models (Table 6.7).

Comorbidity was strongly related to survival. For colon cancer, two-year survival for patients who had spent more than 10 days in hospital in the preceding two years was 44%, compared to 70% for patients who had spent no time in hospital. For rectal cancer patients, the corresponding survival estimates were 40% compared to 68%. Similar differences were observed for comorbidity measured with the Charlson and Scottish indices. Comorbidity did not explain the deprivation-specific gradient in risk of death, however, as inclusion of comorbidity improved the model fit but did not reduce the relative risk of death between affluent and deprived patients.

Health care system factors

Differences in survival between patients treated at specialist and non-specialist hospitals have been reported previously but were accounted for by age and stage at diagnosis^{21,203}. For colon cancer patients diagnosed in Scotland in 1997, two-year survival for patients receiving surgery at regional RT centres was similar to those treated at other hospitals. For surgically treated rectal cancer patients, survival was slightly higher for those treated at regional RT centres (72% compared to an average of 68% at other hospitals).

^f In the north of Scotland study, accessibility was not as much of an issue because access would have been poor for most of the long-distance travellers.

Table 6.7: Patients diagnosed with colorectal cancer in Scotland in 1997: univariate influence of individual factors on the relative risk of death within two-years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analyses)

Variables included in the model ¹	COLON					RECTUM				
	Relative risk ²	95% CI		P-value ³	P-value of added term ⁴	Relative risk ²	95% CI		P-value ³	P-value of added term ⁴
		Low	High				Low	High		
Initial model: Deprivation category	1.13	0.93	1.37	0.211	-	1.75	1.25	2.46	<0.01	-
Patient characteristics:										
Age (null model) ⁵	1.20	0.99	1.46	0.064	<0.001	1.80	1.28	2.52	<0.01	<0.001
Sex	1.21	0.99	1.47	0.058	0.020	1.75	1.25	2.46	<0.01	<0.01
Health board of residence	1.23	0.99	1.52	0.058	0.805	1.93	1.33	2.82	<0.01	0.230
Urban indicator	1.21	0.99	1.49	0.063	0.770	1.79	1.26	2.54	<0.01	0.936
Previous history of primary cancer	1.20	0.99	1.46	0.065	0.623	1.78	1.26	2.49	<0.01	0.315
Bed-days comorbidity score	1.15	0.95	1.41	0.150	<0.001	1.69	1.20	2.37	<0.01	<0.001
Charlson comorbidity score	1.15	0.95	1.40	0.155	<0.001	1.85	1.32	2.60	<0.001	<0.001
Scotland comorbidity score	1.18	0.97	1.43	0.104	<0.001	1.79	1.28	2.51	<0.01	<0.001
Health care system factors:										
Attended a high-workload hospital?	1.18	0.96	1.44	0.108	0.019	1.91	1.35	2.70	<0.001	0.038
Workload of hospital of main treatment	1.17	0.96	1.43	0.121	0.008	1.84	1.30	2.61	<0.01	0.196
Attended a specialist department?	1.19	0.98	1.45	0.078	<0.001	1.89	1.35	2.66	<0.001	<0.001
Emergency admission	1.19	0.98	1.45	0.082	<0.001	1.79	1.28	2.52	<0.01	<0.001
Time to diagnosis to surgery ⁶	1.14	0.90	1.45	0.271	<0.001	1.65	1.05	2.60	0.030	<0.001
Workload of clinician overseeing surgery ⁶	1.14	0.90	1.47	0.270	<0.001	1.57	0.99	2.48	0.051	<0.001
Workload of clinician seen within 3 months	1.21	1.00	1.48	0.052	<0.001	1.80	1.28	2.53	<0.01	0.141
Tumour characteristics:										
Histological verification	1.25	1.03	1.51	0.027	<0.001	1.82	1.30	2.56	<0.01	<0.001
Dukes stage	1.41	1.16	1.72	0.001	<0.001	1.88	1.33	2.66	<0.001	<0.001
Grade	1.28	1.05	1.56	0.013	<0.001	1.77	1.26	2.49	<0.01	<0.001
Tumour histological type	1.28	1.05	1.55	0.014	<0.001	1.79	1.27	2.51	<0.01	<0.001
Treatment factors:										
Treatment intent (curative or palliative)	1.30	1.07	1.88	<0.01	<0.001	1.68	1.19	2.08	<0.01	<0.001
Surgery (yes or no)	1.19	0.98	1.45	0.075	<0.001	1.74	1.23	2.46	<0.01	<0.001
Radiotherapy (yes or no)	1.21	1.00	1.47	0.056	0.024	1.89	1.34	2.67	<0.001	0.095
Chemotherapy (yes or no)	1.21	0.99	1.47	0.060	0.797	1.82	1.30	2.57	<0.01	0.194
Treatment combination (see Table 6.6)	1.24	1.02	1.51	0.029	<0.001	1.74	1.24	2.46	<0.01	<0.001

¹ Each categorical variable is added separately to the null model,

² Significance of the difference in the relative risk between affluent and deprived,

³ Significance of the age term is tested against a model containing deprivation category,

⁴ Relative risk of death in the deprived compared to affluent group

⁵ Improvement in model fit when each variable is added to the null model

⁶ These analyses only include surgically treated patients

After adjusting for age and stage at diagnosis, rectal cancer patients treated at regional RT centres had significantly higher survival than patients treated at other hospitals (data not shown). When surgical and non-surgical cases are considered together, the deprivation-specific differences in risk of death for patients with rectal cancer was unaffected by hospital workload (RR 1.84; Table 6.7).

Colorectal cancer patients who didn't attend a specialist department had significantly poorer survival than those who did (21% compared to 58%). This may be because older (aged 80+) patients and those with very early (Dukes' A) or very late (Dukes' D) stage tumours were less likely to attend a specialist department.

Survival from colorectal cancer is substantially influenced by the presence of complications, such as obstruction and perforation, which are more commonly associated with advanced tumours, and are especially pertinent for emergency admissions²⁰⁴. For patients diagnosed in Scotland during 1997, those who presented as an emergency did have a significantly poorer outlook, with survival for colon cancer patients of 42% for those admitted as an emergency compared to 60% for those admitted routinely, and survival for rectal cancer patients of 33% compared to 63%. Patients admitted as an emergency were more likely to be elderly (65% were aged 70+, compared to 56% of elective admission patients), more likely to have Dukes' B-D tumours (95% compared to 84%) and less likely to receive surgery (21% compared to 14%).

For colon cancer patients, those seen within 3 months of diagnosis by a medium-high workload (≥ 20 cases) clinician had significantly higher survival at 2 years after diagnosis (61%) than those seen by a medium-workload clinician (10-19 cases; 53%) or low-workload clinician (< 10 cases; 45%; $p < 0.001$). For rectal cancer, survival of patients seen by a medium-high workload clinician was 62% compared to 63% for those seen by medium-workload clinician and 54% for those seen by a low-workload clinician ($p = 0.030$). This was true for elective and emergency admission patients, and was particularly evident for patients with higher stage (Dukes' C and D) tumours. If a high-workload clinician was managing the patient at the time of surgery survival was higher (68% compared to 56% for low-workload clinicians for colon cancer patients; 94% compared to 68% for medium- and low-workload clinicians for rectal cancer patients; $p = 0.036$).

Hospital and clinician workload appeared to be independently important. Patients treated in high-workload hospitals did better if seen by a high-workload clinician (2-year survival of 78% compared to 58% for patients seen by a low-workload clinician in a high-workload hospital; $p < 0.01$). A similar pattern was seen for patients treated in medium-workload hospitals, but was not repeated in low-workload hospitals.

For colon cancer patients, all of the health care system factors improved the model fit, but did not affect the relative risk of death between affluent and deprived patients (Table 6.7). For rectal cancer patients, all the health care factors with the exception of the hospital of treatment and clinician workload improved the model fit, but again, none of the factors explained the deprivation-specific differences in the relative risk of death. Adjusting for the workload of the clinician managing the patient at the time of surgery appeared to explain some of the differences in deprivation-specific survival for rectal cancer patients (RR for surgical patients reduced from 1.66 to 1.57).

Tumour characteristics

Survival within two-years was 88% for patients with Duke A tumours, 76% with Dukes' B, 58% with Dukes' C, 11% with Dukes' D, and 20% for patients with unknown stage. These survival estimates are more favourable than those reported in the UK in the early 1990s^{180,181}, suggesting that general improvements seen in survival over time are due to improvements in treatment within each stage as well as to earlier diagnosis, as previously noted^{188,189}. Differences in survival between deprivation groups have been identified in previous studies^{13,17,38,147}, and were not accounted for by stage at diagnosis¹⁷ or delay^{38,147}. Similarly in the Scottish data, adjusting for differences in stage at diagnosis did not explain the increased risk of death in deprived compared to affluent patients (for colon cancer patients the RR increased from 1.20 to 1.41; for rectal cancer patients the RR increased from 1.75 to 1.88).

Tumour grade is another important prognostic indicator, and differences in survival by grade were particularly marked for colon cancer patients (78% for patients with well-differentiated tumours, 64% for patients with moderately-differentiated, and 37% for patients with poorly-differentiated or undifferentiated tumours). In contrast for rectal cancer, patients with well-differentiated or moderately-differentiated tumours had similar survival (68%) compared to 50% for those with poorly-differentiated or undifferentiated tumours. For both cancer sites, only a third of patients with unknown grade survived for

two years, and almost half of these patients did not receive surgery. Survival varied between deprivation groups for colon cancer patients with unknown grade (28% for affluent compared to 16% for deprived) but there was no clear pattern across the deprivation groups.

Patients with histologically verified tumours had significantly better survival than patients whose tumours were not histologically verified ($p < 0.001$). Colon cancer patients with adenocarcinomas had slightly better survival than patients with mucinous tumours (59% compared to 54%), and patients with other or unspecified tumour types had significantly worse survival (12%). For rectal cancer patients the difference in survival between histological types was more marked (63% for patients with adenocarcinomas, 45% for patients with mucinous tumours, and 5% for patients with other and unspecified types).

Inclusion of tumour characteristics including histological verification, stage, grade and histological type, improved the model fit for both colon and rectal cancer patients (Table 6.7). For colon cancer patients, taking into account differences in tumour characteristics actually increased the deprivation-specific differences in risk of death and rendered the difference significant. For rectal cancer patients, the differences in risk of death were also enhanced by inclusion of information on tumour characteristics in the model. Missing stage and grade makes interpretation of these models more difficult; however, the results were similar if only patients with known stage and grade were included in the analysis (data not shown).

Treatment factors

Patients who were treated with curative intent had significantly better two-year survival (83%) than those treated with palliative intent (19%) or for whom the treatment intent was unknown (55%). Survival was also related to the type of treatment received, with better survival for patients receiving surgery compared to no surgery, chemotherapy compared to no chemotherapy, and conversely, no radiotherapy compared to radiotherapy. However, treatment options are not independent of patient and tumour characteristics, or hospital and consultant. Patients receiving radiotherapy followed by surgery and chemotherapy had the best survival (81%), then patients receiving radiotherapy followed by surgery (73%), surgery alone or with chemotherapy (63%), surgery followed by radiotherapy and chemotherapy (56%), surgery followed by radiotherapy (46%), chemotherapy alone (24%), radiotherapy

alone (19%), or chemotherapy and radiotherapy in combination (9%). Inclusion of surgery, radiotherapy, treatment combinations and treatment intent information all improved the model fit, but did not explain differences in survival between affluent and deprived patients (Table 6.7). Inclusion of information on treatment for colon cancer patients accentuated the differences in the risk of death between affluent and deprived patients. For rectal cancer patients, the deprivation-specific risk of death was largely unchanged when adjustment was made for differences in treatment.

Multivariate analyses

In the main multivariate analyses the factors were grouped into patient characteristics, health care system factors, tumour characteristics and treatment factors (Table 6.8; only factors that improved the model fit are displayed) and each factor examined allowing for all related factors (models 1-4). Deprivation group and age were included in each model. The significant factors in each of these group models were then included in the final model (model 5; Table 6.9).

In model 1, age and the bed-days comorbidity score were important patient-related factors improving the model fit. For colon cancer patients, Charlson comorbidity score and the Scottish comorbidity score were also important prognostic indicators independently of each other. For rectal cancer patients, sex was an important prognostic indicator. Information on health board of residence, rurality of residence and history of cancer did not improve the fit of the model once age, comorbidity and sex had been included. For colon cancer patients, differences in age and comorbidity did not explain the deprivation-specific differences in the risk of death (RR remained 1.13). For rectal cancer patients, differences in age, sex and comorbidity explained around 10% of the deprivation-specific differences in risk of death (RR reduced from 1.75 to 1.66; Table 6.8).

Model 2 included the health care system factors, and type of admission (emergency or elective), whether seen in a specialist department, whether seen (for rectal) or treated (for colon) in a high-workload hospital or regional RT centre, whether a high-workload clinician was managing the patient at the time of surgery, and the length of time between diagnosis and treatment all improved the model fit, so were important in explaining survival variations.

Table 6.8: Patients diagnosed with colorectal cancer in Scotland in 1997: multivariate influence of all the factors grouped on the relative risk of death within two years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analyses)

Model	COLON				RECTUM			
	Relative risk	95% CI Low	95% CI High	P-value	Relative risk	95% CI Low	95% CI High	P-value
Model 0: Deprivation only								
Dep1: Affluent	1.00				1.00			
Dep2	0.95	0.79	1.15	0.619	1.23	0.88	1.73	0.223
Dep3	0.86	0.71	1.04	0.118	1.28	0.91	1.79	0.155
Dep4	1.05	0.86	1.27	0.648	1.46	1.04	2.06	0.029
Dep5: Deprived	1.13	0.93	1.37	0.211	1.75	1.25	2.46	<0.01
Model 1: Demographic factors								
Dep1: Affluent	1.00				1.00			
Dep2	1.00	0.83	1.20	0.978	1.18	0.84	1.66	0.328
Dep3	0.85	0.70	1.04	0.110	1.17	0.84	1.64	0.360
Dep4	1.04	0.86	1.26	0.683	1.26	0.89	1.78	0.187
Dep5: Deprived	1.13	0.92	1.37	0.239	1.66	1.18	2.33	<0.01
Ages 20-49 (colon) / 30-44 (rectum)	1.00				1.00			
Ages 50-59 / 45-49	1.10	0.74	1.63	0.645	1.66	0.57	4.87	0.356
Ages 60-69 / 50-59	1.17	0.82	1.68	0.390	1.01	0.39	2.62	0.989
Ages 70-74 / 60-69	1.47	1.02	2.12	0.037	1.65	0.66	4.09	0.282
Ages 75-79 / 70-79	1.78	1.24	2.54	<0.01	2.41	0.98	5.92	0.054
Ages 80-84 (colon and rectum)	2.05	1.43	2.95	<0.001	2.89	1.15	7.25	0.024
Ages 85+ (colon and rectum)	3.17	2.20	4.56	<0.001	6.80	2.72	16.99	<0.001
Males	-				1.00			
Females	-				0.72	0.58	0.89	<0.01
No bed-days	1.00				1.00			
1-4 bed-days	1.42	1.10	1.84	<0.01	1.02	0.74	1.39	0.916
5-10 bed-days	1.75	1.36	2.25	<0.001	1.58	1.12	2.24	<0.01
11+ bed-days	1.89	1.53	2.33	<0.001	2.02	1.55	2.64	<0.001
No comorbidity (Charlson index)	1.00				-			
Comorbidity (Charlson index)	1.39	1.16	1.68	<0.001	-			
No comorbidity (Scottish index)	1.00				-			
Comorbidity (Scottish index)	1.23	1.04	1.45	0.013	-			
Model 2: Health care system factors^{1,2}								
Dep1: Affluent	1.00				1.00			
Dep2	1.07	0.89	1.30	0.469	1.18	0.83	1.68	0.352
Dep3	0.93	0.77	1.13	0.470	1.26	0.89	1.79	0.184
Dep4	1.03	0.85	1.26	0.738	1.32	0.93	1.89	0.124
Dep5: Deprived	1.14	0.93	1.39	0.202	1.75	1.23	2.48	<0.01
Routine admission	1.00				1.00			
Emergency admission	1.53	1.34	1.74	<0.001	2.10	1.65	2.68	<0.001
Admission type unknown	0.71	0.39	1.29	0.256	0.44	0.15	1.32	0.142
Not seen in a specialist department	1.00				1.00			
Seen in a specialist department	0.71	0.58	0.87	0.001	0.51	0.35	0.75	<0.01
Treated in a regional RT centre ³	1.00				1.00			
Treated at a high-workload hospital ³	1.13	0.92	1.39	0.237	1.11	0.77	1.61	0.577
Treated at a med-high workload hosp ³	0.99	0.83	1.17	0.871	0.77	0.57	1.04	0.094
Treated at a med-low workload hosp ³	1.04	0.86	1.25	0.678	0.81	0.58	1.13	0.208
Treated at a low-workload hospital ³	0.71	0.55	0.92	<0.01	0.54	0.35	0.82	<0.01
Not treated in a hospital ³	1.26	0.63	2.54	0.513	2.75	0.98	7.68	0.054
Low-workload clinician at surgery ⁴	1.00				1.00			
Med-low workload clinician at surgery ⁴	0.87	0.72	1.04	0.119	1.00	0.73	1.36	0.985
Med-high workload clinician at surgery ⁴	0.68	0.55	0.85	<0.01	0.89	0.62	1.30	0.360
High-workload clinician for surgery ⁴	0.66	0.40	1.08	0.098	0.10	0.01	0.75	0.025
Patient didn't have surgery	1.23	0.94	1.60	0.137	1.70	1.22	2.36	<0.01

Table 6.8 continued.

Model	COLON				RECTUM			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 2 continued..								
<2 weeks wait for treatment	1.00				1.00			
>2 weeks wait for treatment	0.81	0.69	0.94	<0.01	0.74	0.57	0.97	0.029
No treatment received	3.12	2.33	4.19	<0.001	1.73	1.15	2.59	<0.01
Model 3: Presentation factors^{2,3}								
Dep1: Affluent	1.00				1.00			
Dep2	1.01	0.84	1.22	0.908	1.17	0.83	1.64	0.362
Dep3	1.03	0.85	1.25	0.740	1.33	0.95	1.87	0.099
Dep4	1.25	1.03	1.52	0.023	1.47	1.04	2.08	0.028
Dep5: Deprived	1.42	1.17	1.73	<0.001	1.88	1.33	2.66	<0.001
Dukes A	1.00				1.00			
Dukes B	2.16	1.32	3.51	<0.01	1.87	1.15	3.04	0.011
Dukes C	4.43	2.74	7.16	<0.001	3.13	1.96	4.99	<0.001
Dukes D	16.22	10.04	26.20	<0.001	13.88	8.77	21.97	<0.001
Unknown stage	12.52	7.70	20.37	<0.001	8.22	5.18	13.04	<0.001
Grade 1	1.00				-			
Grade 2	1.32	0.83	2.11	0.235	-			
Grade 3/4	2.48	1.55	3.98	<0.001	-			
Unknown grade	2.28	1.43	3.64	<0.01	-			
Model 4: Treatment factors²								
Dep1: Affluent	1.00				1.00			
Dep2	1.09	0.91	1.32	0.352	1.21	0.86	1.70	0.278
Dep3	1.00	0.82	1.21	0.965	1.24	0.88	1.75	0.216
Dep4	1.13	0.93	1.37	0.211	1.39	0.98	1.97	0.064
Dep5: Deprived	1.32	1.09	1.61	<0.01	1.58	1.11	2.23	0.010
Curative treatment intent	1.00				1.00			
Palliative treatment intent	7.83	6.58	9.33	<0.001	8.07	6.00	10.85	<0.001
Unknown treatment intent	3.48	2.57	4.71	<0.001	3.70	2.11	6.50	<0.001
Surgery alone	1.00				1.00			
Radiotherapy alone	4.40	2.06	9.36	<0.001	1.01	0.67	1.51	0.962
Pre-treatment RT, surgery & chemo	0.22	0.03	1.54	0.126	0.43	0.17	1.08	0.073
Surgery and radiotherapy	1.07	0.73	1.56	0.745	1.35	0.89	2.04	0.160
Surgery and chemotherapy	0.70	0.56	0.87	<0.01	0.86	0.52	1.43	0.561
Other treatment combinations	1.09	0.83	1.42	0.542	0.85	0.61	1.19	0.348
No treatment	2.59	2.20	3.06	<0.001	1.55	1.14	2.13	<0.01

¹ The workload of clinician seen within three months of diagnosis variable was also significant for colon cancer patients but is excluded because it was those with unknown clinician workload who had differing survival

² Age is also included in these models but results not presented on the table

³ For rectal cancer patients it was the workload of the hospital the patient attended within three months of diagnosis that was important rather than the workload of the hospital of treatment

⁴ This is the workload of the clinician overseeing the patient at the time they had surgery – they may not have been present at or performed the surgery.

⁵ Tumour type was also significant in these models but is excluded because it was those with unknown tumour type who had the different survival

After accounting for these factors, additional information on whether the patient saw a high-workload clinician within 3 months of diagnosis did not improve the model fit. Remarkably, after adjusting for differences in all these health care system factors between affluent and deprived patients, there was still no change in the deprivation-specific differences in the risk of death for either colon or rectal cancer patients.

In model 3, stage and grade were important prognostic indicators for colon cancer patients. For rectal cancer patients, stage was a very important prognostic indicator, and grade was no longer an important prognostic indicator in a model that included stage. Whether the tumour was microscopically verified and the histological type of the tumour did not influence survival after adjusting for stage and grade (Table 6.8). After adjusting for differences in stage and grade, the deprivation-specific survival gradient became bigger, particularly for colon cancer patients (RR increased from 1.13 to 1.42), indicating that the null model was masking inequalities. If patients with unknown grade and stage were excluded from the analysis the deprived patients with colon cancer still had a higher risk of death than affluent patients (RR=1.24; $p=0.10$) but the difference was not significant. For rectal cancer patients, it is perhaps surprising that differences in the distribution of stage at presentation, an extremely important prognostic indicator, do not explain the deprivation-specific differences in survival (RR increases from 1.75 to 1.88). However, stage-by-stage, survival was higher for affluent than deprived patients with rectal cancer.

Final model: colon cancer

Colon cancer patients from deprived areas did not appear to have a survival disadvantage compared to affluent patients when the data were initially examined, however, after adjusting for the factors that had the strongest influence on survival, including age, comorbidity, type of admission (elective or emergency), tumour stage and grade, treatment received and whether surgery was overseen by a high-workload clinician, there was a significant difference in the risk of death for deprived compared to affluent patients (RR=1.33; $p<0.01$; Table 6.9). This difference was reduced (from 1.33 to 1.19) and non-significant if patients with information on missing stage were excluded, an important consideration because stage and grade were more likely to be missing for affluent patients. Stage-by-stage survival was similar for affluent and deprived patients with colon cancer; however, deprived patients with missing stage had significantly lower survival than patients from the other deprivation groups with missing stage ($p<0.01$). If the "real" stage distribution differed across the deprivation groups for patients with stage missing then the risk estimate of 1.33 would be biased. This is explored further in the discussion.

Table 6.9: Patients diagnosed with colorectal cancer in Scotland in 1997: multivariate influence of all the significant factors combined on the relative risk of death within two years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analyses)

Model	COLON				RECTUM			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 5: Final model¹								
Dep1: Affluent	1.00				1.00			
Dep2	1.06	0.88	1.29	0.526	1.04	0.73	1.49	0.810
Dep3	0.96	0.79	1.17	0.679	1.18	0.83	1.67	0.350
Dep4	1.10	0.90	1.33	0.365	1.27	0.88	1.83	0.201
Dep5: Deprived	1.33	1.09	1.62	<0.01	1.41	0.98	2.04	0.066
No bed-days	-				1.00			
1-4 bed-days	-				1.14	0.82	1.57	0.439
5-10 bed-days	-				1.47	1.02	2.11	0.040
11+ bed-days	-				1.45	1.09	1.93	0.011
No comorbidity (Charlson index)	1.00				-			
Comorbidity (Charlson index)	1.25	1.02	1.52	0.032	-			
No comorbidity (Scottish index)	1.00				-			
Comorbidity (Scottish index)	1.26	1.06	1.50	<0.01	-			
Routine admission	1.00				1.00			
Emergency admission	1.34	1.18	1.53	<0.001	1.62	1.26	2.09	<0.001
Admission type unknown	1.30	0.76	2.25	0.341	0.65	0.21	2.05	0.463
Seen in a regional RT centre	-				1.00			
Seen at a high-workload hospital	-				1.74	1.17	2.58	<0.01
Seen at a med-high workload hosp	-				1.16	0.85	1.59	0.358
Seen at a med-low workload hosp	-				1.15	0.82	1.62	0.428
Seen at a low-workload hospital	-				0.87	0.56	1.35	0.525
Not seen in a hospital	-				2.50	0.87	7.21	0.090
Not seen in a specialist department	-				1.00			
Seen in a specialist department	-				0.41	0.28	0.60	<0.001
Low-workload clinician at surgery ²	1.00				-			
Med-low workload clinician at surgery ²	0.91	0.76	1.09	0.317	-			
Med-high workload clinician at surgery ²	0.75	0.60	0.94	0.012	-			
High-workload clinician at surgery ²	0.87	0.53	1.42	0.574	-			
Patient didn't have surgery	0.95	0.70	1.28	0.723	-			
<2 weeks wait for treatment	1.00				1.00			
>2 weeks wait for treatment	0.81	0.70	0.95	<0.01	0.70	0.53	0.93	0.014
No treatment received	0.97	0.46	2.06	0.942	0.87	0.59	1.27	0.467
Dukes A	1.00				1.00			
Dukes B	2.11	1.29	3.46	<0.01	1.41	0.86	2.33	0.172
Dukes C	3.14	1.92	5.16	<0.001	1.78	1.07	2.95	0.026
Dukes D	5.39	3.27	8.86	<0.001	3.56	2.08	6.09	<0.001
Unknown stage	3.96	2.39	6.56	<0.001	2.27	1.33	3.88	<0.01
Grade 1	1.00				-			
Grade 2	1.02	0.64	1.63	0.922	-			
Grade 3	1.78	1.10	2.87	0.018	-			
Unknown grade	1.48	0.91	2.39	0.110	-			
Curative treatment intent	1.00				1.00			
Palliative treatment intent	4.63	3.76	5.69	<0.001	5.14	3.67	7.19	<0.001
Unknown treatment intent	2.23	1.60	3.09	<0.001	1.90	1.04	3.47	0.037
Surgery alone	1.00				-			
Radiotherapy alone	3.14	1.40	7.07	<0.01	-			
Pre-treatment RT, surgery & chemo	0.21	0.03	1.50	0.120	-			
Surgery and radiotherapy	1.12	0.77	1.64	0.557	-			
Surgery and chemotherapy	0.58	0.46	0.73	<0.001	-			
Other treatment combinations	0.93	0.68	1.27	0.633	-			
No treatment received	1.88	0.88	4.00	0.102	-			

¹ Age is also included in this model but the results not presented on the table

² This is the workload of the clinician overseeing the patient at the time they had surgery – they may not have been present at or performed the surgery.

Final model: rectal cancer

Rectal cancer patients from deprived areas had a significantly lower survival than affluent patients in the null model, and after adjusting for the factors that had the strongest influence on survival from rectal cancer, including age, comorbidity, type of admission (emergency or elective), specialty and workload of the hospital attended, whether seen in a specialist department, tumour stage and treatment intent, almost a half of the difference in risk of death between affluent and deprived patients was explained (RR reduced from 1.75 to 1.41), and the difference was rendered marginally non-significant (Table 6.9). There was still a clear trend across the deprivation groups, and although the difference in the risk was non-significant a 40% increased risk of death is clearly important, and with a larger sample of patients, to give more power to detect differences, may well have remained significant.

Discussion

Differences in survival between socio-economic groups for both colon and rectal cancer have been reported elsewhere^{13,17,38,147}. For the patients diagnosed in Scotland in 1997, survival prospects also differed by deprivation group. On the surface, the differences appear small for colon cancer patients but large (12% at two years) for rectal cancer patients. There were no major differences between the deprivation groups in age at diagnosis, sex, tumour stage or tumour grade at diagnosis. However, deprived patients had a higher proportion of metastatic tumours, worse comorbidity at diagnosis, and were also less likely to attend a regional RT centre, be treated in a high-workload hospital or see a high-workload clinician within 3 months of diagnosis. They were also less likely to receive any form of treatment. These differences were all more pronounced for rectal cancer patients.

Colon cancer

The interpretation of the colon cancer results hinges on the validity of stage, particularly because of the large difference in survival between deprived and affluent patients for whom stage was not recorded. Affluent patients were more likely than deprived patients to have no stage recorded, which is surprising, and for these patients, survival was significantly better for affluent than deprived patients. This was not explained by a better stage-specific survival for affluent patients, because survival was similar for all the deprivation groups within each stage.

Our results provide some evidence for the interpretation that the increased risk of death for deprived patients (RR 1.33) is not simply an artefact. Firstly, around 60% of patients with no stage recorded received no treatment, and this did not vary by deprivation group. Secondly, if we consider model 4 (Table 6.8) which does not include grade or stage, a significantly increased risk of death of a similar magnitude to the final model was observed (RR 1.32 compared to 1.33), after adjustment for treatment intent and the combination of treatment(s) received. Since treatment choice is strongly related to stage, this lends support to the validity of the 33% excess risk of death in deprived patients.

Given the large effect of stage on deprivation-specific differences in survival, stage migration should be mentioned. For example, if radiological equipment is not available at one hospital or histology is poorly reported, then less rigorous investigations may lead to a patient being erroneously classified with an earlier stage tumour. In this situation, survival becomes apparently worse in the earlier stage to which these tumours are allocated, and (possibly) also in the group of patients with more advanced stage, from which they have been withdrawn, since the remaining patients, on average, have more advanced disease. Incomplete staging would lead to some patients being given inappropriate treatment; even stage-adjusted survival results would be biased as a result of this and stage migration. Stage migration is unlikely to be responsible for the enhanced difference in the risk of death between affluent and deprived patients here, because survival did not vary by deprivation group within each stage.

Stage was collected by the cancer registry for the first time for patients diagnosed in 1997, and a subsequent exercise to assess the quality of these new data highlighted problems in recording (see Chapter 2). For 5% of colorectal cancer patients, stage was not recorded on SOCRATES but it was found in the medical records on re-abstraction by the quality assurance team. Discrepancies in the recording of stage were identified for a further 6% of patients. If some cancer registration officers abstracting data in hospitals seeing mainly affluent patients were inefficient at extracting the stage information, this could explain why this information was more often missing for affluent patients. For patients diagnosed in 1998, stage recorded is more often, and in contrast to 1997, is more often not recorded for deprived patients (17% compared to 13% of affluent patients). Before conclusions can be drawn regarding the observed deprivation-specific differences in survival for colon cancer patients, the analyses in this chapter should be repeated for patients diagnosed in 1998.

Some other important results should also be highlighted. Firstly, after adjusting for case-mix factors, patients receiving surgery and chemotherapy had a significantly better outlook than patients receiving other combinations of treatment (Table 6.9). Adjuvant chemotherapy in the management of colorectal cancer has been clearly linked to outcome, and the national guidelines recommending the use of chemotherapy were published in June 1997; however, only 38% of patients with Dukes' C tumours received chemotherapy in 1997. The provision of chemotherapy was related to whether the patient was seen by a high-workload clinician. Secondly, the workload of the clinician responsible for the patient at the time they had surgery was clearly linked to outcome, even after adjusting for case-mix and treatment. This provides some empirical support to the national initiative to centralise colorectal cancer services.

Evidence of the effect of hospital and clinician workload and specialisation is conflicting, and usually relates to colorectal cancer combined. A Scottish study²⁸ found a significant difference for patients treated by specialist and non-specialist surgeons. Improved survival was observed in Finland for colon cancer patients treated in teaching and non-teaching hospitals, but this was largely explained by differences in age and stage²⁰³. In East Anglia, higher survival for patients treated at cancer centres than those treated at all other hospitals was explained by differences in age, sex and stage for colon cancer, but not for rectal cancer. The remaining difference for rectal cancer patients was restricted to patients aged under 75³¹. A Northern Ireland study¹⁷⁹ found that the workload of the treating hospital but not of the surgeon had a significant impact on survival at two years, after adjusting for other significant factors (age, sex, stage, grade, type of admission and treatment intent). Patients treated in Northern Ireland hospitals with workloads above 33 cases per year had worse survival than those treated in hospitals with smaller workloads. I will refer back to this when discussing the rectal cancer analyses. A similar study conducted on patients diagnosed in the north-west of England¹⁷⁷ found no influence of hospital or clinician workload after adjusting for other significant factors (age, stage, grade and type of admission). This study also found no effect of operator grade (consultant versus junior).

A small Edinburgh study investigated outcomes for 306 consecutive patients referred to one general surgeon. There were no differences in 30-day mortality or survival for patients whose operations were performed by the consultant compared to those who were operated

on by supervised or independent trainees²⁰⁵. In a similar study in East Anglia²⁰⁶, outcomes for patients treated by a general surgeon were compared with those treated by a colorectal specialist in one hospital were audited. There was no difference in overall survival, but the specialist had a lower clinical leak rate and lower rate of palliative diversionary surgery.

In the Northern Ireland study, surgeons dealing with 15 or more cases per year managed only 44% of patients. In comparison, for patients diagnosed in Scotland in 1997, only 28% of patients were seen by high-workload clinicians (here defined as dealing with 20 or more cases per year). The workload of the clinician managing the patient at the time of surgery was shown to be an important prognostic factor, with a better outcome for high-workload than low-workload clinicians. Although patients treated at low-workload hospitals appeared to have a survival advantage when factors relating to hospital services were considered alone (Model 2), this advantage was reduced, and no longer statistically significant, after accounting for comorbidity, stage, grade and treatment received.

Rectal cancer

Rectal cancer patients who were seen in a regional RT centre, seen by a high-workload clinician within 3 months of diagnosis, and whose surgery was overseen by a high-workload clinician, all had a survival advantage when these factors were looked at individually (i.e. no adjustment for other factors). Deprived patients were less likely than affluent patients to fall in these groups, and differences in survival between affluent and deprived patients appeared to be partly explained by the workload of the clinician managing the patient at the time of surgery when considered alone (Table 6.7). This not only resulted in a higher post-operative mortality for deprived patients, but was also evident if only patients who had already survived at least 1 month were considered (data not shown).

When all the factors relating to the health care system were considered alone (Model 2), whether the patient attended a high-workload hospital or regional RT centre was an important factor, but it was in the low-workload hospitals that patients appeared to fare the best. This was probably an artefact of case-mix, because in the final model containing all significant factors, the difference was smaller, and non-significant. Why patients seen at high-workload hospitals other than regional RT centres had significantly poorer survival is not clear, although it may be because those patients deemed well enough for adjuvant therapy were sent to a regional RT centre rather than to other high-workload hospitals.

This would also explain why treatment does not appear to be an important prognostic indicator in the final model, which would otherwise be surprising, given the importance of chemotherapy for rectal cancer patients. Treatment decisions are not independent of specialisation/workload, clinical and other case-mix factors. Despite the move to centralise surgery for rectal cancer patients since 1996, only 39% of rectal cancer patients diagnosed in 1997 received their surgery in a high-workload hospital. After adjusting for hospital workload, clinician workload was no longer a significant prognostic indicator, even though surgery for rectal cancer patients is a highly specialised intervention. In the model including only hospital factors, patients managed by high-workload clinicians had a very large survival advantage compared to those managed by low-workload clinicians (RR 0.10; Model 2). The magnitude of the difference was similar if this factor was included in the final model, but it was no longer significant. This may be due to the relatively small sample size for the rectal cancer analysis (844 patients). After adjusting for age and stage at diagnosis, rectal cancer patients treated at regional RT centres had significantly higher survival than patients treated at other hospitals.

Deprived patients with rectal cancer were less likely to receive any treatment (18% received no treatment compared to 11% of affluent patients). The proportion of rectal cancer patients with Dukes' C tumours receiving chemotherapy (41%) was lower than might be expected, with very large variation between deprivation groups (52% of affluent and 30% of deprived patients). For patients with Dukes' C tumours, where a clear link between chemotherapy and outcome has been made, inequalities in treatment of this magnitude should not exist.

It is interesting to note that of the 17% of patients who did not receive any treatment, half of them only saw a low-workload clinician. This may reflect their physical state or might indicate that low-workload consultants are not providing appropriate treatment(s). Deprived patients treated with curative intent had significantly lower survival than affluent patients (two-year survival: 77% compared to 91%), as did those treated with palliative intent (21% compared to 29%). Affluent patients were significantly more likely to have unknown treatment intent, but even if we assume all the patients with unknown treatment intent were treated with curative intent, the deprived patients still have worse survival (77% compared to 88%). So, deprived patients do worse whether they are treated with palliative or curative intent, and they are less likely to receive treatment.

Deprived rectal cancer patients were also more likely to have metastatic tumours at diagnosis (21% compared to 15% of patients in all the other deprivation groups combined) which may explain why they were less likely to receive any treatment. This was also true for patients diagnosed in 1998 (26% of deprived compared to 21% of affluent patients had metastatic disease at presentation). Tumour stage is clearly an important prognostic factor in the final model (Table 6.9), and it is interesting that grade is no longer an important prognostic indicator after adjusting for stage. Insofar as deprivation-specific differences in survival are stage-dependent, then mass screening might help reduce inequalities in survival, although deprivation-specific differences in compliance and the poor reliability of the FOB test make this by no means a certainty²⁰⁷.

General

Overall, the distribution of stage at diagnosis appears to have improved over time. The Scottish cancer registry did not collect information on tumour stage prior to 1997; however, comparing the stage distribution with that observed in Scottish audits conducted in the early 1990s, patients diagnosed in 1997 were less likely to present with metastatic disease, even though similar proportions were still presenting as an emergency. Also, within each tumour stage, survival for patients diagnosed in 1997 appears higher than that reported in previous audits. Given the fact that fewer patients are presenting with metastatic disease and stage-specific survival is improving, the trend for improved survival from colorectal cancer (see Figure 6.4) is likely to be due both to earlier diagnosis and to improvements in treatment, including peri-operative care.

A minor point that may be worth noting is that two-year survival for colorectal cancer was significantly worse ($p=0.04$) for patients diagnosed in December than in other months of the year (48.2% compared to 54.8%). This appears to echo a study in Finland in which patients treated during holiday periods had worse survival than those treated at other times¹³⁷.

In conclusion, for colon cancer, deprived patients had a small (13%) and non-significant excess mortality compared to affluent patients, which increased to 33% after adjustment for differences in the main prognostic factors: age, comorbidity, clinician workload, stage, grade and treatment. However, it is hard to rule out the possibility of artefact in the recording of

stage by deprivation group, and this relatively small excess cannot confidentially be ascribed to differences in clinician workload, tumour characteristics and treatment in these data.

For rectal cancer, there was a 75% excess risk of death in deprived compared to affluent patients, and a clear gradient across the deprivation groups. This excess was reduced to 40% by adjusting for differences in comorbidity, type of admission (emergency or elective), hospital specialty and workload, stage and treatment intent. This difference was statistically non-significant but it is clearly important. Repeating the analyses on a larger sample of patients, with more complete data on prognostic variables, would help elucidate these remaining differences, and determine if deprivation-related differences in survival can be explained by differences in access to care and treatment.

BLADDER AND KIDNEY CANCERS

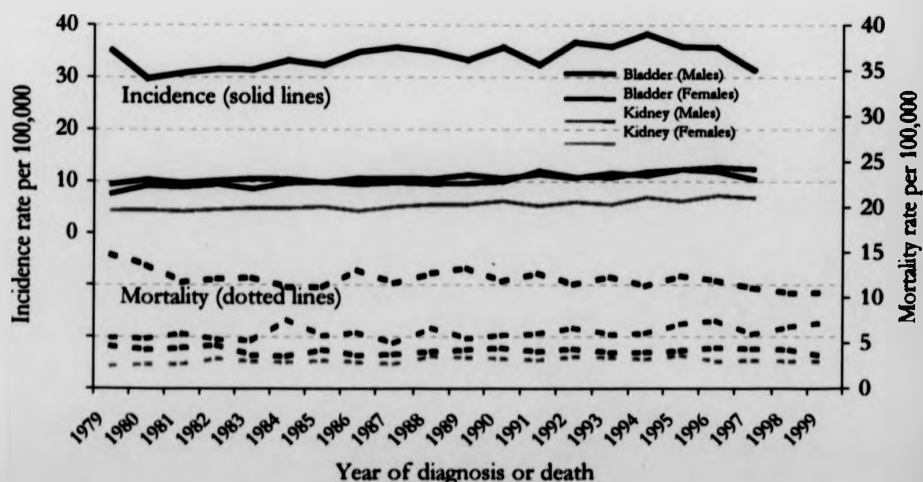
Background

Bladder and kidney cancers are examined together in this chapter as they comprise most (94%) of the urinary tract, have similar aetiology, are both managed by urologists, and have similar treatment regimes.

Bladder cancer

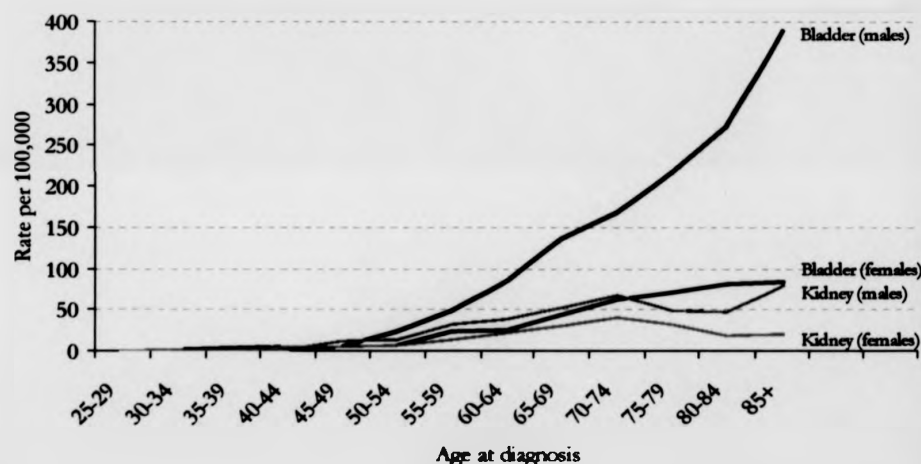
Bladder cancer is the 4th most common cancer among men (7.7% of all cancers) and the 7th most common cancer among women (3.4%) in Scotland. In 1997, a total of 1 208 new cases were diagnosed. Incidence has been increasing over time since around 1980 for both sexes although this shows signs of reversing in recent data (Figure 7.1). This recent decline is thought to be a cohort effect and is occurring across all age groups^{208,209}.

Figure 7.1: Cancers of the bladder and kidney in Scotland: trends in incidence (1979-97) and mortality (1979-99), all ages (European age-standardised rates)



Incidence of bladder cancer in Scotland is significantly higher in men than women at all ages, and the gap between the sexes increases with age. The risk in men aged over 80 years is more than four-fold that in women of the same age (Figure 7.2). The majority of bladder cancers are transitional cell carcinomas, which are known to be associated with cigarette smoking and occupational exposure to certain carcinogens²⁰⁸, so the difference in incidence between the sexes may be due to occupational and lifestyle factors²¹⁰.

Figure 7.2: Age-specific incidence of bladder and kidney cancer in Scotland, patients diagnosed in 1997, by sex

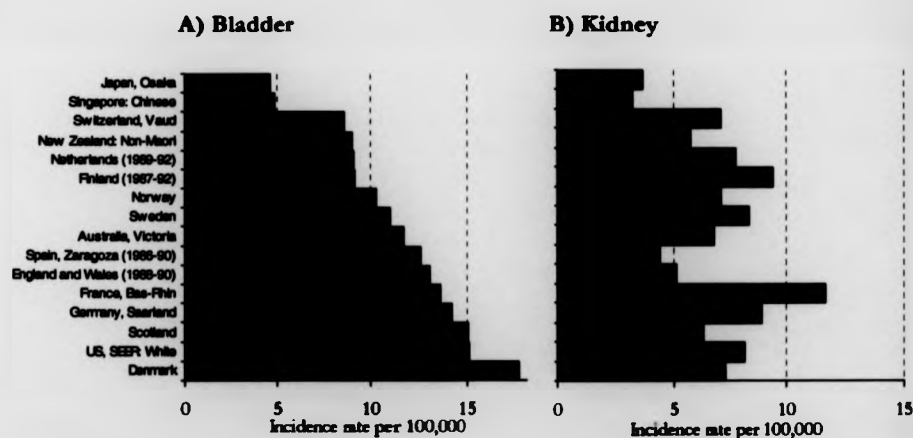


Incidence of bladder cancer is higher in Scotland than in most other European countries (Figure 7.3). However, this may be a reflection of local practices in the registration of 'benign' bladder tumours or 'papillomas', since there is no standardisation of coding of non-invasive tumours to take into account recorded level of invasion and grade²¹¹. An increase in the registration of small papillomas as malignant may explain the high rates of bladder cancer in men in Scotland, particularly in older men, as they will receive investigative procedures for urinary symptoms more frequently.

Over the next decade the incidence of bladder cancer is expected to decline slightly in Scotland, although the numbers of cases is predicted to increase due to the ageing population, with the gap between males and females widening still further¹⁵².

Mortality from bladder cancer has declined slightly in males over the last 20 years (by around 1% per year since 1979), and the rates for females have remained stable (Figure 7.1). In 1999, 449 patients died of bladder cancer in Scotland. Mortality rates and numbers of deaths are expected to continue to decline in males, and to begin to decline in females, over the next decade¹⁵².

Figure 7.3: International comparison of bladder and kidney cancer incidence, around 1988-92 (world age-standardised rates), both sexes combined



Source: Cancer Incidence in Five Continents, Vol. VII⁸⁸

Unusually, survival from bladder cancer is higher for males than females. This may, again, be due to an excess of papillomas being diagnosed in males. A study in the USA found that females did have a slightly higher proportion of worse stage tumours, but this did not appear to completely explain their poorer outcome, because survival was higher for males within each stage²¹².

In Scotland, survival has improved for patients diagnosed over the last 28 years, with one-year survival increasing from 70% to 78% in males, and from 61% to 67% in females. Similar improvements are seen at five years after diagnosis from around 55% to 68% in males and from 49% to 61% in females (Figure 7.4). Survival is most favourable at younger ages, and is higher in males than females at all ages, but particularly in the elderly (ages 75 and over)¹. Survival from bladder cancer in Scotland is similar to the average of that seen in Europe although significantly lower than some European countries and the USA (Figure 7.5). These geographical comparisons, however, are difficult to interpret due to the coding problems surrounding invasive bladder cancers.

Kidney cancer

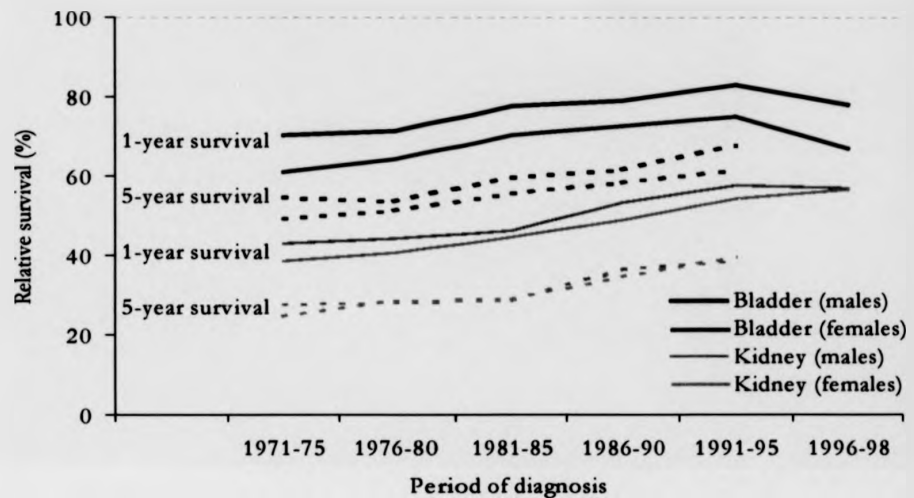
Kidney cancer is the 10th most common cancer among men (2.5% of all cancers) and the 15th most common cancer among women (1.7% of all cancers) in Scotland. Incidence has been increasing gradually since around 1980 (see Figure 7.1), and in 1997 a total of 486 new cases were diagnosed in Scotland. As for bladder cancer, the disease is more common in males than females at all ages (see Figure 7.2).

Kidney cancer in adults is rare in Scotland compared to most other European countries or the USA, with lower incidence observed only in Asia, England and Wales, and Spain, of the countries compared (see Figure 7.3). Tobacco smoking is thought to be one of the major causes, especially for renal pelvis tumours, with a moderately increased risk due to obesity and a western type diet; however, these factors do not explain the low rates in Scotland. The incidence of kidney cancer is predicted to increase by around 50% in the next decade¹⁵², which will raise the public health importance of these tumours.

Mortality from kidney cancer has increased slightly over the last 20 years (see Table 7.1), and in 1999 a total of 304 patients died of kidney cancer in Scotland.

Survival from kidney cancer has improved over time, but even now fewer than 40% of patients are alive five years after diagnosis. One-year survival has increased from 41% to 60% and five-year survival has increased from 26% to 39% from 1971-75 to 1991-95 (Figure 7.4). Survival is similar between the sexes, and decreases with increasing age in both sexes.

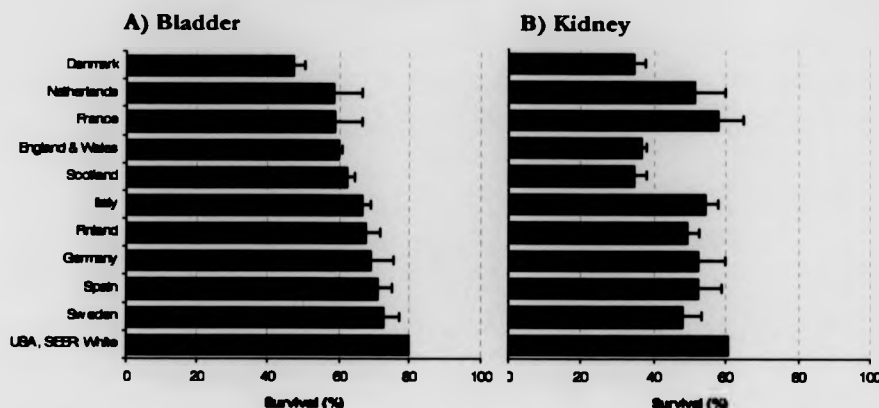
Figure 7.4: Patients diagnosed with bladder and kidney cancer in Scotland during 1971-98: trends in relative survival by sex



Survival from kidney cancer is significantly worse in Scotland than in most other European countries and the USA (Figure 7.5).

In this chapter the survival of 1 694 patients diagnosed with bladder or kidney cancer in Scotland in 1997 is investigated to identify reasons for differences in survival by deprivation category. For definitions of the variables included in the analyses, please refer to Chapter 2.

Figure 7.5: Bladder and kidney cancer: international comparison of five-year relative survival (with 95% confidence intervals), selected countries, patients diagnosed around 1985-89, all ages¹



Sources: Berrino *et al.*⁴, Coleman *et al.*⁴, SEER²¹⁵

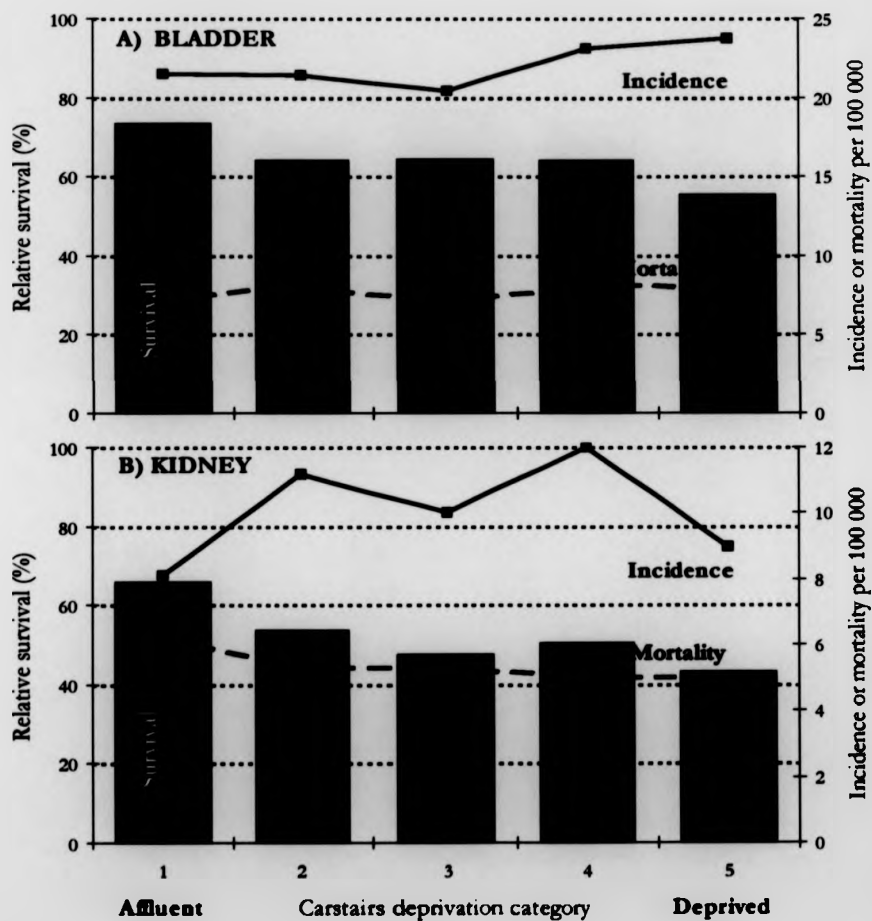
¹ Patients diagnosed 1986-90 aged 15-99 in England and Wales; patients aged 15-99 in Scotland; patients diagnosed 1988-92 in USA.

Results and commentary

Incidence of bladder and kidney cancer was broadly similar across deprivation groups for Scottish residents in 1997 (Figure 7.6). There was little variation in mortality across the deprivation groups for bladder cancer. For kidney cancer, higher mortality was observed for affluent compared to deprived patients, but the numbers on which this is based are relatively small. Two-year survival was significantly higher in affluent compared to deprived patients with bladder cancer (73% compared to 55%) and kidney cancer (66% compared to 43%).

Bladder cancer has previously been reported to be more common in deprived groups of patients^{1,208}. This was not observed for patients diagnosed in Scotland in 1997, but may reflect small numbers in analysing data from only one year. Studies looking at incidence and deprivation for kidney cancer have not identified a clear relationship^{1,214}. Previous studies of socio-economic differences in survival have consistently shown deprived patients with bladder cancer and with kidney cancer to have poorer survival than affluent patients^{4,33,43,215,217}. However, studies looking at social variations in survival for these cancers are sparse.

Figure 7.6: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: incidence¹ and relative survival², and mortality¹ in 1999, by deprivation category



¹ Age-standardised rates per 100,000 person-years at risk (European standard population).

² Using deprivation-specific life tables; age-standardised to the world standard cancer patient population.

Bladder and kidney cancers were more common in men, who made up 68% of bladder and 59% of kidney cancer patients in 1997 (Table 7.1). For bladder cancer, the proportion of males was similar across the deprivation groups, however, for kidney cancer there were significantly fewer males in the deprived group (47% compared to 68% in the affluent group). The distribution of age at diagnosis was similar across deprivation groups for bladder cancer patients, with a median age of 72 years. The median age at diagnosis for kidney cancer patients was 68 years, and patients from deprived areas tended to present at an older age than affluent patients (not significant).

Bladder or kidney cancer was the first primary malignancy for 1 535 (91%) of patients, with 6 patients having two cancers diagnosed simultaneously, 7 having a previous primary at the same site, and 146 having had a previous primary at another site.

Less than half (41%) of patients came from urban areas, and because deprived areas in Scotland are largely urban, deprived patients with bladder and kidney cancer were more likely to come from urban areas (Table 7.1).

Organisation of services

UK guidelines recommend that patients with suspected urological malignancy be referred to cancer centres in large hospitals with the necessary facilities available²¹⁸. Adequate access to radiological and treatment facilities are essential. Multidisciplinary teams are important in the management of bladder and kidney cancer patients, and should comprise urologists with oncological expertise and clinical oncologists (for patients with advanced disease). Rapid diagnosis in patients with haematuria can be achieved via haematuria clinics with "one-stop" visits for cystoscopy and upper urinary tract imaging²¹⁹. Cystoscopic surveillance is needed for patients with superficial disease¹⁵².

Of the patients diagnosed in Scotland in 1997, only 46% of bladder and 45% of kidney cancer patients attended a regional RT centre at some point during their cancer spell. Deprived patients with kidney cancer were significantly less likely to attend a regional RT centre than affluent patients (Table 7.2). Despite the recommendations in the guidelines, 17% of bladder and 23% of kidney cancer patients were *only* seen in a medium-low or low-workload hospital.

Table 7.1: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: demographic data by deprivation category (number and percentage of cases)

Deprivation category	No. of patients		No. of females ¹		Median age (inter-quartile range)	Cases for which:				No. of urban residents ²
						First primary	Simultaneous primary	Previous primary at same site	Previous primary elsewhere	
Bladder										
Affluent	255	(21%)	89	(35%)	73 (65-79)	229 (90%)	0 (0%)	2 (1%)	24 (9%)	93 (36%)
2	239	(20%)	65	(27%)	72 (63-79)	214 (90%)	0 (0%)	0 (0%)	25 (10%)	55 (23%)
3	220	(18%)	68	(31%)	73 (65-80)	194 (88%)	0 (0%)	1 (0%)	25 (11%)	59 (27%)
4	248	(21%)	78	(31%)	72 (64-78)	230 (93%)	2 (1%)	1 (0%)	15 (6%)	98 (40%)
Deprived	246	(20%)	88	(36%)	71 (65-78)	224 (91%)	0 (0%)	1 (0%)	21 (9%)	190 (77%)
Total	1,208	(100%)	388	(32%)	72 (65-79)	1,091 (90%)	2 (0%)	5 (0%)	110 (9%)	495 (41%)
Kidney										
Affluent	81	(17%)	26	(32%)	64 (56-72)	74 (91%)	0 (0%)	0 (0%)	7 (9%)	36 (44%)
2	112	(23%)	44	(39%)	66 (58-74)	99 (88%)	1 (1%)	1 (1%)	11 (10%)	23 (21%)
3	97	(20%)	36	(37%)	69 (61-72)	92 (95%)	0 (0%)	0 (0%)	5 (5%)	27 (28%)
4	110	(23%)	47	(43%)	68 (61-76)	98 (89%)	3 (3%)	1 (1%)	8 (7%)	50 (45%)
Deprived	86	(18%)	46	(53%)	69 (61-73)	81 (94%)	0 (0%)	0 (0%)	5 (6%)	71 (83%)
Total	486	(100%)	199	(41%)	68 (59-73)	444 (91%)	4 (1%)	2 (0%)	36 (7%)	207 (43%)
Total	1,694	(100%)	587	(35%)	70 (63-77)	1,535 (91%)	6 (0%)	7 (0%)	146 (9%)	702 (41%)

¹ Chi-square test for association between sex and deprivation group for kidney cancer: $p=0.059$

² Chi-square test for association between urban residence and deprivation group for bladder and kidney cancer: $p<0.001$

Affluent patients were more likely to receive their main treatment (defined as surgery or earliest other treatment for non-surgical patients) in a regional RT centre than deprived patients with bladder cancer (34% compared to 25%; $p=0.03$) or kidney cancer (56% compared to 29%; $p<0.001$). Overall, only 27% of bladder and 38% of kidney cancer patients were treated in a regional RT centre. This is in contrast to patients diagnosed in East Anglia during 1989-93, where 55% of bladder cancer patients were treated in a regional RT centre³¹. For the Scottish data, the proportion of patients (56%) treated in any high-workload hospital (regional RT centre or other high-workload hospital) varied significantly by deprivation group but with no clear trend. Kidney cancer patients were slightly less likely (52%) to be treated in a high-workload hospital than bladder cancer patients, and affluent patients were more likely than deprived to be treated in a high-workload hospital (not significant).

Overall, 80% of bladder cancer patients attended a specialist department within three months of diagnosis, and deprived patients were actually more likely to attend a specialist department ($p<0.001$). For kidney cancer, 63% of patients attended a specialist department, and affluent patients were significantly more likely to attend a specialist department ($p<0.01$) compared to the other deprivation groups.

A quarter (24%) of bladder and 11% of kidney cancer patients were seen by a high-workload consultant within three months of diagnosis, and deprived patients were less likely to be seen by a high-workload consultant (bladder: $p=0.047$; kidney: $p=0.428$). Of the 904 surgically treated bladder cancer patients with consultant details, 61% of affluent compared to only 48% of deprived patients were managed at surgery by a medium- or high-workload clinician (managing at least 20 bladder cases per year; not significant). For the 227 surgically-treated kidney cancer patients with consultant details, 79% of affluent and 67% of deprived patients were managed by a medium- or high-workload consultant (managing at least 5 kidney cancer cases per year; not significant).

Table 7.2: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: access to health care by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Attended a regional RT centre ¹	Attended a specialist department ²	Main treatment at a regional RT centre ³	Treated in a high-workload hospital ⁴	Seen by a high-workload consultant ⁵	Emergency admission	More than two weeks' delay between diagnosis and treatment ⁶
Bladder								
Affluent	255	121 (47%)	192 (75%)	87 (34%)	148 (58%)	65 (25%)	48 (19%)	135 (62%)
2	239	105 (44%)	179 (75%)	61 (26%)	101 (42%)	64 (27%)	49 (21%)	132 (63%)
3	220	105 (48%)	185 (84%)	66 (30%)	139 (63%)	48 (22%)	40 (18%)	120 (62%)
4	248	110 (44%)	202 (81%)	56 (23%)	118 (48%)	69 (28%)	47 (19%)	144 (68%)
Deprived	246	115 (47%)	206 (84%)	61 (25%)	165 (67%)	43 (17%)	52 (21%)	128 (65%)
Total	1,208	556 (46%)	964 (80%)	331 (27%)	671 (56%)	289 (24%)	236 (20%)	659 (64%)
Significance ⁷		$p=0.875$	$p<0.001$	$p=0.03$	$p<0.001$	$p=0.047$	$p=0.931$	$p=0.497$
Kidney								
Affluent	81	50 (62%)	63 (78%)	45 (56%)	50 (62%)	10 (12%)	32 (40%)	49 (69%)
2	112	54 (48%)	62 (55%)	44 (39%)	53 (47%)	11 (10%)	33 (29%)	55 (72%)
3	97	39 (40%)	57 (59%)	33 (34%)	49 (51%)	15 (15%)	35 (36%)	48 (75%)
4	110	47 (43%)	68 (62%)	40 (36%)	60 (55%)	11 (10%)	32 (29%)	58 (78%)
Deprived	86	31 (36%)	54 (63%)	25 (29%)	41 (48%)	6 (7%)	32 (37%)	44 (75%)
Total	486	221 (45%)	304 (63%)	187 (38%)	253 (52%)	53 (11%)	164 (34%)	254 (74%)
Significance ⁷		$p<0.01$	$p=0.03$	$p<0.001$	$p=0.280$	$p=0.428$	$p=0.477$	$p=0.148$

¹ At some point during their cancer spell

² Within 3 months of diagnosis

³ Number of patients whose main treatment was performed at a regional RT centre (surgery, or earliest treatment for non-surgical patients)

⁴ Hospital seeing at least 49 bladder or 18 kidney cancer patients (highest workload quartile; see Chapter 2 for workload bandings)

⁵ Consultant seeing at least 30 bladder or 10 kidney cancer patients (highest workload quartile); percentage of those with consultant details, seen by consultant within 3 months of diagnosis (see Chapter 2 for workload bandings)

⁶ Days between diagnosis and definitive treatment; percentage of those with a definitive treatment date

⁷ Chi-square test for association

Delay

The most frequent primary symptom for bladder or kidney cancer is macro- or microscopic haematuria, and patients with this symptom are generally referred to a urologist. Further primary symptoms for kidney cancer are loin pain or a palpable mass. Secondary effects include weight loss, fever, back pain, anaemia and general malaise. Only a third of patients present with primary symptoms and so there is often a delay in diagnosis, which is reflected in the emergency admission rates.

For patients diagnosed in Scotland in 1997, 20% of bladder and 34% of kidney cancer patients were admitted as an emergency (Table 7.2). There was no trend in the proportion of emergency admissions across the deprivation groups. Older patients were significantly more likely to be admitted as an emergency (34% aged 80 and over compared to 21% aged under 50). Grade was also an important factor, with 26% of patients with grade 3 tumours compared to 14% of patients with grade 1 tumours presenting as an emergency.

For two-thirds of bladder and three-quarters of kidney cancer patients, at least two weeks elapsed between diagnosis and definitive treatment. The median wait for treatment was higher for kidney cancer patients in the most deprived group (41 days) compared to the other deprivation groups (32 days; data not shown). There were no differences between deprivation groups in time to surgery for bladder cancer patients.

Mode of presentation

When a patient presents with a suspected bladder cancer they will usually receive an endoscopic examination (cystoscopy) and upper urinary tract imaging in the form of intravenous urogram or ultrasound. Patients with suspected kidney cancer receive non-invasive imaging such as ultrasound, CT scanning or MRI.

Pathological tumour stage and lymph node status are the most important prognostic indicators for bladder cancer²²⁰. Around 70% of bladder tumours are superficial and the rest invasive²²¹. For patients diagnosed with invasive bladder cancer in East Anglia during 1989-93, 47% were stage 1 tumours, 25% were stage 2, 20% were stage 3, and 9% were stage 4 tumours. For localised kidney cancers, tumour size is an important prognostic indicator²²², but kidney cancer is characterised by few early warning signs, so 20-30% of patients present

with metastases at diagnosis²²³. Information on stage for bladder and kidney cancers is not available on SOCRATES.

Grade and histological type are also important prognostic indicators^{223,224}, in particular grade for clear-cell kidney cancer. For patients diagnosed in Scotland in 1997, 19% of bladder and 67% of kidney cancer patients had unknown grade. Of patients with known grade, only a quarter of bladder and one-tenth of kidney cancer patients presented with well-differentiated tumours (Table 7.3). There were differences in grade at presentation across the deprivation groups for bladder cancer patients, but the pattern was unclear.

Table 7.3: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: grade by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Grade ¹			
		1	2	3/4	Unknown
Bladder					
Affluent	255	42 (20%)	82 (40%)	81 (40%)	50 (20%)
2	239	58 (30%)	48 (25%)	86 (45%)	47 (20%)
3	220	43 (22%)	61 (31%)	91 (47%)	25 (11%)
4	248	46 (23%)	70 (36%)	80 (41%)	52 (21%)
Deprived	246	53 (28%)	62 (33%)	74 (39%)	57 (23%)
Total	1,208	242 (25%)	323 (33%)	412 (42%)	231 (19%)
<i>Significance²</i>		<i>p=0.090³</i>			<i>p=0.023⁴</i>
Kidney					
Affluent	81	3 (12%)	11 (42%)	12 (46%)	55 (68%)
2	112	5 (15%)	17 (50%)	12 (35%)	78 (70%)
3	97	3 (9%)	13 (39%)	17 (52%)	64 (66%)
4	110	4 (10%)	24 (57%)	14 (33%)	68 (62%)
Deprived	86	2 (7%)	14 (52%)	11 (41%)	59 (69%)
Total	486	17 (10%)	79 (49%)	66 (41%)	324 (67%)
<i>Significance²</i>		<i>p=0.822³</i>			<i>p=0.767⁴</i>

¹ Percentage of patients with a known category, except 'unknown', presented as a percentage of the total

² Chi-square test for association

³ Significance of association across the deprivation categories excluding those in the unknown category

⁴ Significance of proportion unknown across the deprivation categories

Diagnosis was microscopically verified for most bladder (96%) and kidney (79%) cancer patients, and these proportions did not vary significantly across the deprivation groups (Table 7.4). Most of the bladder cancers were transitional cell tumours (93%), and around half of these were papillary. There were no differences in histological type between the deprivation groups for bladder cancer patients. Over two-thirds (68%) of the kidney cancer

patients presented with renal cell carcinomas, 20% with clear cell tumours and 12% with other cell types. Deprived patients were less likely to present with clear cell tumour (10% compared to 20% overall). A further 5% of bladder and 17% of kidney cancer patients had tumours of unspecified histological type.

Figure 7.4: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: microscopic verification and histological type by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Microscopically verified	Histological type			
			Papillary Transitional Cell	Other Transitional Cell	Other	Unspecified
Bladder						
Affluent	255	247 (97%)	110 (45%)	119 (49%)	16 (7%)	10 (4%)
2	239	228 (95%)	100 (44%)	107 (47%)	21 (9%)	11 (5%)
3	220	212 (96%)	92 (43%)	110 (52%)	10 (5%)	8 (4%)
4	248	238 (96%)	103 (44%)	119 (50%)	14 (6%)	12 (5%)
Deprived	246	231 (94%)	111 (48%)	101 (44%)	17 (7%)	17 (7%)
Total	1,208	1,156 (96%)	516 (45%)	556 (48%)	78 (7%)	58 (5%)
<i>Significance¹</i>		<i>p=0.542</i>			<i>p=0.610</i>	<i>p=0.265</i>

Deprivation category	No. of patients	Microscopically verified	Histological type			
			Renal cell	Clear cell	Other	Unspecified
Kidney						
Affluent	81	69 (85%)	48 (68%)	12 (17%)	11 (15%)	10 (12%)
2	112	86 (77%)	66 (71%)	19 (20%)	8 (9%)	19 (17%)
3	97	76 (78%)	51 (60%)	25 (29%)	9 (11%)	12 (12%)
4	110	83 (75%)	53 (62%)	19 (22%)	14 (16%)	24 (22%)
Deprived	86	68 (79%)	55 (80%)	7 (10%)	7 (10%)	17 (20%)
Total	486	382 (79%)	273 (68%)	82 (20%)	49 (12%)	82 (17%)
<i>Significance¹</i>		<i>p=0.563</i>			<i>p=0.093</i>	<i>p=0.272</i>

¹ Percentage of patients with a known category; except 'unknown', presented as a percentage of the total

² Chi-square test for association

³ Significance of association between deprivation category and percentage of patients in each category excluding those in the unknown category

⁴ Significance of proportion unknown across the deprivation categories

There was a relationship between grade and histological type for both cancers. For bladder cancer, 38% of patients with papillary tumours had well-differentiated tumours compared to 14% of patients with other transitional cell tumours; 22% of the papillary and 59% of the other transitional cell tumours were poorly-differentiated or undifferentiated. For kidney cancer, around 50% of patients with renal and clear cell tumours had moderately-

differentiated tumours; however, patients with clear cell tumours were more likely to have well-differentiated tumours (19% compared to 7% of patients with renal cell tumours).

Comorbidity

Overall, 25% of bladder and 38% of kidney cancer patients had spent more than 10 days in hospital in the two years preceding the cancer diagnosis. Comorbidity was lower when measured with the disease-based (Scotland or Charlson) indices compared to the bed-days index. For bladder cancer, deprived patients had somewhat higher comorbidity than affluent patients at the time of diagnosis with all three comorbidity measures, but none was significant (Table 7.5). There was no pattern in comorbidity across the deprivation groups for kidney cancer patients.

Figure 7.5: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: comorbidity and post-operative mortality by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Comorbidity			30 day post-operative mortality ⁴
		Bed-days ¹	Scotland ²	Charlson ³	
Bladder					
Affluent	255	59 (23%)	41 (16%)	27 (11%)	6 (3%)
2	239	56 (23%)	42 (18%)	23 (10%)	3 (2%)
3	220	57 (26%)	44 (20%)	26 (12%)	2 (1%)
4	248	61 (25%)	52 (21%)	30 (12%)	2 (1%)
Deprived	246	68 (28%)	53 (22%)	35 (14%)	2 (1%)
Total	1,208	301 (25%)	232 (19%)	141 (12%)	15 (2%)
<i>Significance⁵</i>		<i>p=0.767</i>	<i>p=0.482</i>	<i>p=0.580</i>	<i>p=0.524</i>
Kidney					
Affluent	81	27 (33%)	11 (14%)	8 (10%)	1 (2%)
2	112	45 (40%)	27 (24%)	14 (13%)	1 (1%)
3	97	42 (43%)	24 (25%)	19 (20%)	2 (3%)
4	110	42 (38%)	20 (18%)	15 (14%)	4 (6%)
Deprived	86	31 (36%)	24 (28%)	13 (15%)	3 (6%)
Total	486	187 (38%)	106 (22%)	69 (14%)	11 (4%)
<i>Significance⁵</i>		<i>p=0.498</i>	<i>p=0.148</i>	<i>p=0.419</i>	<i>p=0.406</i>

¹ More than 10 inpatient bed-days in the two years prior to cancer diagnosis

² Any one of certain comorbid conditions recorded in the two years prior to one month after diagnosis (see Chapter 1)

³ Any one of certain comorbid conditions recorded in the five years prior to diagnosis (see Chapter 1)

⁴ Percentage of patients undergoing surgery (998 bladder cancer patients; 298 kidney cancer patients)

⁵ Chi-square test for association

Treatment

Surgical resection is the primary treatment for bladder cancer (a cystectomy) and kidney cancer (a nephrectomy) patients with localised disease. For locally advanced kidney cancer the surgery can be more complex and is best provided in specialist centres. For bladder cancer patients with tumours confined to the bladder wall, cystectomy with extended pelvis lymph node dissection has been shown to improve prognosis²²⁵. Surgical resection is also considered for metastatic tumours especially clear cell kidney tumours.

Patients with localised tumours may receive pre-operative radiotherapy to reduce the tumour size. Post-operative radiotherapy or chemotherapy may be given following radical surgery, and for bladder cancer, chemotherapy after surgery has been shown to give a better prognosis than radiotherapy after surgery. Chemotherapy or radiotherapy may also be given as palliation for advanced bladder or kidney disease. Hormone therapy may also be for specific rare tumour types.

For patients diagnosed in Scotland in 1997, 82% of bladder and 61% of kidney cancer patients received surgery (Table 7.6). A quarter (26%) of bladder cancer patients received radiotherapy (21% within 6 months of diagnosis) compared to 14% of kidney cancer patients (12% within 6 months). Twelve percent of bladder cancer patients received chemotherapy (9% within 6 months) compared to only 4% of kidney cancer patients. Only two patients received neo-adjuvant chemotherapy and 10 patients received neo-adjuvant radiotherapy.

Deprived patients were significantly less likely to receive surgery alone as treatment for bladder cancer (41% compared to 58% of affluent patients; $p=0.011$) or kidney cancer (49% compared to 65%; $p=0.039$; Table 7.7). Deprived patients were more likely to receive radiotherapy alone or, for bladder cancer, radiotherapy in combination with surgery. Deprived patients with bladder cancer were also more likely to receive no treatment (15% compared to 9% of affluent patients).

Table 7.6: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: treatment and timings by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Surgery		Radiotherapy		Chemotherapy		Hormone therapy	
		Within 6 months	Overall	Within 6 months	Overall	Within 6 months	Overall	Within 6 months	Overall
Bladder									
Affluent	255	208 (82%)	215 (84%)	48 (19%)	63 (25%)	22 (9%)	26 (10%)	7 (3%)	8 (3%)
2	239	191 (80%)	198 (83%)	42 (18%)	56 (23%)	19 (8%)	28 (12%)	1 (0%)	1 (0%)
3	220	183 (83%)	188 (85%)	44 (20%)	55 (25%)	20 (9%)	28 (13%)	3 (1%)	3 (1%)
4	248	203 (82%)	204 (82%)	52 (21%)	61 (25%)	24 (10%)	36 (15%)	1 (0%)	2 (1%)
Deprived	246	179 (73%)	183 (74%)	68 (28%)	81 (33%)	20 (8%)	28 (11%)	2 (1%)	2 (1%)
Total	1,208	964 (80%)	988 (82%)	254 (21%)	316 (26%)	105 (9%)	146 (12%)	14 (1%)	16 (1%)
Significance ^a		p=0.160	p=0.091	p=0.301	p=0.443	p=0.727	p=0.524	p=0.313	p=0.267
Kidney									
Affluent	81	59 (73%)	60 (74%)	8 (10%)	12 (15%)	5 (6%)	6 (7%)	2 (2%)	2 (2%)
2	112	68 (61%)	70 (63%)	11 (10%)	14 (13%)	4 (4%)	4 (4%)	4 (4%)	5 (4%)
3	97	57 (59%)	59 (61%)	12 (12%)	12 (12%)	4 (4%)	5 (5%)	6 (6%)	6 (6%)
4	110	59 (54%)	62 (56%)	13 (12%)	14 (13%)	1 (1%)	2 (2%)	6 (5%)	6 (5%)
Deprived	86	44 (51%)	47 (55%)	14 (16%)	16 (19%)	0 (0%)	1 (1%)	3 (3%)	3 (3%)
Total	486	287 (59%)	296 (61%)	58 (12%)	68 (14%)	14 (3%)	18 (4%)	21 (4%)	22 (5%)
Significance ^a		p=0.017	p=0.031	p=0.858	p=0.868	p=0.095	p=0.153	p=0.943	p=0.958

¹ Chi-square test for association

Overall, a higher proportion of kidney than bladder cancer patients received no treatment (27% compared to 11%), and this proportion was similar across the deprivation groups with the exception of the most affluent group where only 9% of bladder cancer and 10% of kidney cancer patients did not receive any treatment.

Table 7.7: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: treatment combinations by deprivation category (number and percentage of cases)

Treatment combinations	Affluent	2	3	4	Deprived
Bladder					
Surgery alone	148 (58%)	134 (56%)	118 (54%)	120 (48%)	100 (41%)
Radiotherapy (RT) alone	12 (5%)	13 (5%)	8 (4%)	12 (5%)	22 (9%)
Surgery and RT	39 (15%)	36 (15%)	39 (18%)	45 (18%)	52 (21%)
Surgery and chemo	15 (6%)	21 (9%)	21 (10%)	33 (13%)	23 (9%)
Other combination	14 (5%)	8 (3%)	8 (4%)	5 (2%)	7 (3%)
Unknown combination	3 (1%)	2 (1%)	4 (2%)	6 (2%)	5 (2%)
No treatment	24 (9%)	25 (10%)	22 (10%)	27 (11%)	37 (15%)
Total	255 (100%)	239 (100%)	220 (100%)	248 (100%)	246 (100%)
Kidney					
Surgery alone	53 (65%)	61 (54%)	52 (54%)	56 (51%)	42 (49%)
Radiotherapy (RT) alone	5 (6%)	7 (6%)	6 (6%)	10 (9%)	10 (12%)
Chemotherapy alone	4 (5%)	3 (3%)	3 (3%)	1 (1%)	0 (0%)
Surgery and RT	4 (5%)	6 (5%)	5 (5%)	2 (2%)	4 (5%)
Other combination	2 (2%)	1 (1%)	2 (2%)	2 (2%)	4 (1%)
Unknown combination	5 (6%)	2 (2%)	1 (1%)	3 (3%)	3 (3%)
No treatment	8 (10%)	32 (29%)	28 (29%)	36 (33%)	26 (30%)
Total	81 (100%)	112 (100%)	97 (100%)	110 (100%)	86 (100%)

Treatment choices varied by age. For bladder cancer, 77% of patients aged 70 and over compared to 88% of younger patients received surgery ($p < 0.001$). Older patients were twice as likely as younger patients to receive no treatment (14% compared to 7%) or radiotherapy alone (7% compared to 3%). For kidney cancer patients the differences were much larger, with 42% of older compared to 16% of younger patients receiving no treatment ($p < 0.001$). Treatment choices also varied by age for patients diagnosed with kidney cancer in The Netherlands in the 1980s²²⁶, with resection rates of 63% in patients aged 70 and over compared to 82% in younger patients; the difference was not accounted for by metastatic status at presentation.

Treatment combination was also significantly related to grade at presentation. For bladder cancer patients, 76% of patients with well-differentiated, 64% with moderately-differentiated and 31% with poorly-differentiated or undifferentiated tumours had surgery alone; 2% with well-differentiated, 11% with moderately-differentiated and 37% of patients with poorly-differentiated or undifferentiated tumours had surgery with RT. The proportion of bladder cancer patients receiving no treatment did not vary according to grade. In contrast, for kidney cancer patients with known grade (this only includes 33% of patients), all patients with well-differentiated tumours and most (90%) patients with moderately-differentiated tumours received surgery alone (4% had no treatment, and 6% other combinations of treatment). Kidney cancer patients with poorly-differentiated or undifferentiated tumours received more varied treatments, including surgery alone (67%), surgery with RT (11%), RT alone (5%), other combinations of treatment (5%) or no treatment (12%).

Radiotherapy after surgery was less likely to be given for papillary than other transitional bladder cancers (11% compared to 25%), but these patients were more likely to receive chemotherapy instead (13% compared to 7%). Overall, bladder cancer patients with papillary tumours were more likely to receive surgery (91% compared to 81% for other transitional cell tumours, 77% for other cell types, and 12% for unspecified cell types).

Bladder cancer patients treated in medium-high workload hospitals were more likely to have received surgery and chemotherapy than those treated elsewhere. Overall, 80% of patients treated in high-workload, 92% in medium-high workload, 86% in medium-low workload, and 64% of patients treated in low-workload hospitals received surgery ($p < 0.01$). The lower rate in high-workload hospitals is partly explained by the referral of non-surgical cases to these centres for other adjuvant treatments. Chemotherapy was given to around 10% of patients in all hospital workload groups, but was more common for patients treated in medium-high workload hospitals (19%). For patients who received surgery, around 25% went on to have radiotherapy and this did not vary by hospital workload, with the exception of those patients treated in small workload hospitals (18% went on to have radiotherapy). For patients who did not receive surgery but had radiotherapy (6% of patients), the hospital of treatment was by definition the regional RT centre (in the high workload hospital group).

Kidney cancer patients treated in low-workload hospitals were also less likely to receive surgery (47% compared to 62% of patients treated in high-workload, 71% in medium-high

workload and 67% in medium-low workload hospitals). Chemotherapy was rarely given outside the regional RT centres.

Treatment intent^a (curative or palliative) was less likely to be recorded for affluent patients; however, for patients with known treatment intent, affluent patients were more likely to be treated with curative intent than deprived patients (68% compared to 60% for bladder cancer patients; 57% compared to 45% for kidney cancer patients; not significant). If only surgically-treated patients are considered, then the proportion whose intent was curative did not vary across the deprivation groups (76% for bladder and 78% for kidney cancer patients, overall). This may indicate that deprived patients are presenting with tumours less amenable for surgery, or that they have inequitable access to treatment.

Post-operative mortality

The 30-day post-operative mortality rate was 2% for bladder cancer patients and 4% for kidney cancer patients. Kidney cancer patients from deprived areas had a higher post-operative mortality rate than those from affluent areas (6% compared to 2%; not significant). Patients whose surgery was managed by a high-workload consultant had lower post-operative mortality (1%, compared to 2% and 4% for those managed by a medium-workload or low-workload consultant, respectively; $p=0.081$). There was no relationship between hospital workload and post-operative mortality rate.

Two-year survival

Univariate analyses

Factors that had an influence on the prognosis of bladder and kidney cancer patients were investigated in Cox proportional hazards regression models. In the initial models containing deprivation only, the relative risk of death within two years of diagnosis was significantly raised for deprived compared to affluent patients with bladder cancer (RR 1.67 (95% CI 1.25-2.24)) and kidney cancer (RR 1.87 (95% CI 1.18-2.96)).

^a Treatment intent is difficult to interpret as it is a very "soft" variable; it is not often stated explicitly in the medical notes and the cancer registration officers may use their own judgement in recording it.

Patient characteristics

Survival was strongly related to age for both bladder and kidney cancers. Two-year survival was significantly higher for patients aged under 50 (85%) than patients aged 80 and over (40%) with bladder cancer. The corresponding figures for kidney cancer were 72% and 24%.

Including age in the model significantly improved the model fit, but because there were no differences in the age distribution by deprivation group, it did not account for the differences in the relative risk of death between affluent and deprived patients. The model containing deprivation and age was used as the null model, and each factor was added and then removed from the null model one at a time to test its significance as a prognostic factor for bladder and kidney cancer (Table 7.8).

Survival was significantly higher for males than females with bladder cancer, even after accounting for age at diagnosis. This appeared to be because females were less likely than males to present with papillary tumours, which have better prognosis (data not shown). There were no differences in survival by sex for kidney cancer patients. As there were no differences in the sex distribution by deprivation group for bladder cancer patients, inclusion of sex in the null model did not improve the model fit.

There were no differences in survival by health board of residence, urban or rural residence, or whether the patient had a history of cancer, either for bladder or kidney cancer patients. Inclusion of these factors in the null models, therefore, did not improve the model fit.

All three measures of comorbidity were related to survival. Survival for bladder cancer patients with a history of at more than 10 days in hospital in the preceding two years was 37% compared to 74% for patients with 4 or less days spent in hospital. The corresponding two-year survival for kidney cancer patients was 42% compared to 60%. Inclusion of comorbidity in the null model, therefore, improved the model fit. However, as there were no differences in the proportion of patients with comorbidity by deprivation group, unsurprisingly, comorbidity did not explain the deprivation-specific differences in the relative risk of death.

Table 7.8: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: univariate influence of individual factors on the relative risk of death within two years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analysis)

Variables included in the model ¹	BLADDER					KIDNEY				
	Relative risk ²	95% CI		P-value ³	P-value of added term ⁴	Relative risk ²	95% CI		P-value ³	P-value of added term ⁴
		Low	High				Low	High		
Initial model: Deprivation category	1.67	1.25	2.24	<0.01	-	1.87	1.18	2.96	<0.01	-
Patient characteristics:										
Age (<i>null model</i>) ⁵	1.91	1.43	2.57	<0.001	<0.001	1.87	1.17	2.96	<0.01	<0.001 ²
Sex	1.91	1.42	2.56	<0.001	0.026	1.96	1.23	3.13	<0.01	0.185
Health board of residence	1.85	1.35	2.55	<0.001	0.238	2.05	1.23	3.41	<0.01	0.763
Urban indicator	2.01	1.48	2.74	<0.001	0.262	1.83	1.14	2.94	0.013	0.711
Previous history of primary cancer	1.91	1.42	2.56	<0.001	0.460	1.89	1.19	3.01	<0.01	0.426
Bed-days comorbidity index	1.81	1.35	2.43	<0.001	<0.001	1.81	1.14	2.87	0.012	0.013
Charlson comorbidity index	1.86	1.38	2.50	<0.001	<0.01	1.75	1.10	2.79	0.019	0.017
Scotland comorbidity index	1.89	1.41	2.54	<0.001	0.024	1.77	1.11	2.82	0.016	0.021
Health care factors:										
Attended a high-workload hospital?	1.93	1.43	2.59	<0.001	<0.001	2.23	1.39	3.59	<0.01	<0.01
Workload of hospital of main treatment	1.99	1.47	2.67	<0.001	0.072	2.19	1.36	3.52	<0.01	0.015
Attended a specialist department?	2.20	1.63	2.98	<0.001	<0.001	1.63	1.02	2.60	0.039	<0.001
Emergency admission	1.72	1.28	2.30	<0.001	<0.001	2.02	1.27	3.23	<0.01	0.001
Time from diagnosis to treatment	1.84	1.37	2.47	<0.001	<0.001	1.31	0.82	2.10	0.257	<0.001
Workload of consultant managing treatment	1.81	1.34	2.43	<0.001	<0.001	1.42	0.89	2.27	0.136	<0.001
Workload of consultant seen within 3 months	1.87	1.39	2.51	<0.001	0.024	1.73	1.09	2.75	0.021	<0.001
Tumour characteristics:										
Histological verification	1.89	1.41	2.53	<0.001	<0.001	1.66	1.04	2.64	0.033	<0.001
Grade	1.91	1.42	2.56	<0.001	<0.001	1.93	1.21	3.07	<0.01	<0.001
Histological type	1.98	1.47	2.66	<0.001	<0.001	1.55	0.97	2.47	0.065	<0.001
Treatment factors:										
Treatment intent (curative or palliative)	1.77	1.31	2.38	<0.001	<0.001	1.86	1.16	2.98	0.010	<0.001
Surgery (yes or no)	1.72	1.28	2.31	<0.001	<0.001	1.23	0.77	1.97	0.395	<0.001
Radiotherapy (yes or no)	1.77	1.32	2.38	<0.001	<0.001	1.88	1.18	3.00	<0.01	<0.001
Chemotherapy (yes or no)	1.93	1.43	2.59	<0.001	0.058	1.95	1.22	3.12	<0.01	<0.01
Hormone therapy (yes or no)	1.92	1.43	2.58	<0.001	0.899	1.79	1.13	2.85	0.014	<0.01
Treatment combination ⁶	1.62	1.21	2.19	<0.01	<0.001	1.25	0.78	2.01	0.354	<0.001

¹ Each categorical variable is added to the null model containing deprivation category and age

² Significance of the difference in the relative risk between affluent and deprived

³ The significance of the age term is tested against the initial model containing only deprivation

⁴ Relative risk of death in the deprived compared to affluent group

⁵ Improvement in model fit when each variable is added to the null model

⁶ See Table 7.7 for treatment combinations

Health care factors

Patients who attended a regional RT centre at some point during their cancer spell, or whose main treatment was at a regional RT centre, had worse survival than those attending or being treated at high-workload or medium-high workload hospitals. However, if only surgically treated patients were considered, then those treated in regional RT centres had better survival than those treated elsewhere (not significant). Patients treated at low-workload hospitals had significantly poorer survival. In a study of patients diagnosed with bladder cancer in East Anglia during 1989-93, patients treated at regional RT centres compared to other district general hospitals also had a survival advantage but this disappeared after adjusting for tumour stage³¹. Differences in the Scottish data may also, therefore, be due to differences in stage at presentation.

For patients diagnosed in Scotland in 1997, those who attended a specialist department had significantly better two-year survival than those who did not, both for bladder cancer (66% compared to 52%) and especially for kidney cancer patients (61% compared to 26%). Deprived patients were significantly less likely to attend a specialist department, and inclusion of this factor in the null model appeared to explain a quarter of the deprivation-specific differences in the relative risk of death for kidney cancer patients (RR reduced from 1.87 to 1.63).

Patients who were admitted as an emergency had significantly ($p < 0.001$) worse survival than patients who were admitted routinely (36% compared to 71% for bladder cancer patients; 40% compared to 56% for kidney cancer patients). Delay between diagnosis and treatment did not influence survival for bladder or kidney cancer patients; however, patients with no delay information - because they received no treatment - had significantly poorer survival than those for whom information on delay was available.

The workload of the consultant managing the patient at the time of the main treatment was related to survival, with higher survival for high-workload consultants. For bladder cancer, 70% of patients managed by high-workload consultants were alive two years after diagnosis, compared to 66% of those managed by medium-high workload, 62% managed by medium-low workload, and 57% of patients managed by low-workload consultants ($p < 0.001$). For kidney cancer patients, two-year survival was 74% for patients managed by high-workload consultants, 64% for medium-workload and 36% for low-workload consultants ($p = 0.024$).

Information on type of admission, delay and consultant workload all improved the model fit. For patients with kidney cancer, delay in diagnosis explained two-thirds of the difference in relative risk of death between affluent and deprived (RR reduced from 1.87 to 1.31) and rendered the difference non-significant ($p=0.257$); consultant workload explained a half of the difference (RR reduced to 1.42; $p=0.136$). These two factors were only significant prognostic indicators because they had a category "unknown" for patients who did not receive any treatment, so the reduction in risk of death between affluent and deprived patients is actually explained by the differences in the patients receiving treatment.

Tumour characteristics

Unsurprisingly, patients with microscopically verified tumours had significantly higher survival than patients with tumours not microscopically verified. Patients with poorly-differentiated or undifferentiated tumours had significantly lower survival than those with well-differentiated or moderately-differentiated tumours. For bladder cancer, survival for patients with grade 3-4 tumours was 46% compared to 75% for patients with grade 2 tumours and 88% for patients with grade 1 tumours. For kidney cancer patients with known grade (33% of patients), two-year survival was 42% for patients with grade 3-4 tumours, 81% for patients with grade 2 tumours and 100% for patients with grade 1 tumours. Patients with unknown grade had survival estimates similar to those of patients with grade 3-4 tumours. Inclusion of information on microscopic verification and grade in the null model improved the model fit, but did not explain the deprivation-specific differences in the relative risk of death two years after diagnosis.

Survival was better for bladder cancer patients with papillary tumours (81% compared to 55% for other transitional cell tumours, 40% for other cell types, and 33% for unknown cell types). Again, inclusion of this factor in the null model improved the model fit but did not explain the deprivation-specific differences. In contrast, for kidney cancer patients, histological type explained around a third of the difference in the risk of death between affluent and deprived patients (RR reduced from 1.87 to 1.55) and the difference was rendered marginally non-significant ($p=0.065$). The effect of this factor on the deprivation-specific differences was largely explained by whether the patient received treatment, because most (95%) of the unspecified tumours were for patients who did not receive surgery. Patients with clear cell tumours had significantly higher survival than patients with renal cell

tumours (70% compared to 57%), and patients with unknown cell types had significantly worse survival (10%; $p < 0.001$).

Treatment factors

Overall, for bladder cancer, survival was highest for patients receiving surgery alone (79%) or surgery with chemotherapy (81%), compared to surgery with radiotherapy (46%), radiotherapy alone (21%), other treatment combinations (50%) or no treatment (36%). Kidney cancer patients treated with surgery alone also had the highest survival (81%), compared to 33% for surgery with radiotherapy, 3% for radiotherapy alone, 28% for other treatment combinations and 12% for patients who received no treatment. Patients who received hormone therapy had worse survival than those who did not receive hormone therapy, and these were usually non-surgical patients.

For bladder cancer, treatment intent, surgery, radiotherapy and treatment combination improved the model fit when added to the null model, but none of these factors explained the deprivation-specific differences in the risk of death when investigated alone. For kidney cancer, all of the treatment factors improved the model fit, and surgery appeared to explain around two-thirds of the deprivation-specific differences (RR reduced from 1.87 to 1.23; $p = 0.395$). It is probable that deprived patients were presenting with worse prognosis kidney cancers not amenable to treatment, because survival was similar across the deprivation groups for patients who did not receive surgery. If only patients who received surgery are considered, there was still an almost two-fold raised risk of death for deprived compared to affluent patients (data not shown).

Multivariate analyses

In the main multivariate analyses, the factors were grouped into patient characteristics, tumour characteristics, health care system factors and treatment factors (Table 7.9). Each factor was examined allowing for all related factors, and only factors that improved the model fit are presented (models 1-4). Deprivation group and age were included in each model. The significant factors in each of these group models were then included in the final model (Table 7.10; model 5).

In model 1 the important prognostic indicators for both bladder and kidney cancer patients were age and the bed-days comorbidity index. Sex, health board of residence, urban indicator, history of cancer, and the Charlson and Scottish comorbidity indices were not important prognostic indicators in a model containing age and bed-days score. However, the model containing age and bed-days score did not explain the difference in relative risk of death between affluent and deprived bladder or kidney cancer patients. For bladder cancer patients the relative risk of death for deprived compared to affluent patients increased from 1.67 to 1.81, and for kidney cancer the risk remained virtually unchanged.

Among the health care factors included in model 2, type of admissions (routine or emergency), whether the patient was seen in a specialist department, hospital of treatment, and time between diagnosis and treatment were all important explanatory variables. For bladder cancer, the relative risk of death in deprived compared to affluent patients increased after accounting for these factors (from 1.67 to 2.17). This effect was caused by a very strong deprivation-specific gradient in survival among the 244 (20%) of patients who did not attend a specialist department. Patients who did not attend a specialist department would be expected to be those with very good or very bad prognosis tumours, and in these data 84% of the affluent compared to 18% of the deprived patients were treated with curative intent. This indicates large differences in tumour stage by deprivation group for this subset of patients.

For kidney cancer, the relative risk of death in deprived compared to affluent patients was reduced by around 40% (from 1.87 to 1.51; $p=0.105$) and became non-significant in a model containing factors on whether the patient was seen in a specialist department, their hospital of treatment workload and time from diagnosis to treatment. This reduction was due to inclusion of time from diagnosis to treatment as a factor in the model; in particular, whether or not the patient received any treatment. Patients with more than two weeks wait between diagnosis and treatment had better survival than those waiting less than two weeks. This, again, is probably a reflection of tumour stage at diagnosis with treatment being performed more urgently for the worse prognosis cancers and for patients admitted as an emergency.

Table 7.9: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: multivariate influence of groups of factors on the relative risk of death among deprived compared to affluent patients (Cox proportional hazards regression analysis)

Model Variables included in the model	BLADDER				KIDNEY			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 0: Null model								
Dep1: Affluent	1.00				1.00			
Dep2	1.15	0.84	1.58	0.369	1.59	1.01	2.49	0.045
Dep3	1.23	0.89	1.68	0.205	1.78	1.13	2.81	0.013
Dep4	1.27	0.93	1.72	0.128	1.77	1.13	2.77	0.013
Dep5: Deprived	1.67	1.25	2.24	<0.01	1.87	1.19	2.96	<0.01
Model 1: Patient characteristics								
Dep1: Affluent	1.00				1.00			
Dep2	1.21	0.88	1.66	0.236	1.63	1.04	2.57	0.034
Dep3	1.17	0.86	1.61	0.319	1.77	1.12	2.81	0.015
Dep4	1.34	0.98	1.81	0.063	1.72	1.09	2.70	0.019
Dep5: Deprived	1.81	1.35	2.43	<0.001	1.81	1.14	2.87	0.012
<i>Bladder</i>								
Ages 30-49	1.00				1.00			
Ages 50-59	0.87	0.35	2.17	0.768	1.70	0.93	3.09	0.082
Ages 60-69	1.76	0.77	4.04	0.179	2.13	1.19	3.82	0.011
Ages 70-79	2.56	1.13	5.80	0.024	2.67	1.39	5.12	<0.01
Ages 80+	4.60	2.03	10.45	<0.001	3.88	2.05	7.37	<0.001
<i>Kidney</i>								
Ages 00-49	1.00				1.00			
Ages 50-64	0.87	0.35	2.17	0.768	1.70	0.93	3.09	0.082
Ages 65-74	1.76	0.77	4.04	0.179	2.13	1.19	3.82	0.011
Ages 75-79	2.56	1.13	5.80	0.024	2.67	1.39	5.12	<0.01
Ages 80+	4.60	2.03	10.45	<0.001	3.88	2.05	7.37	<0.001
No bed-days	1.00				1.00			
1-4 bed-days	0.92	0.69	1.24	0.589	0.85	0.54	1.32	0.460
5-10 bed-days	1.10	0.80	1.51	0.553	1.33	0.88	2.00	0.179
11+ bed-days	2.48	1.90	3.24	<0.001	1.46	1.02	2.10	0.037
Model 2: Health care factors^{1,2}								
Dep1: Affluent	1.00				1.00			
Dep2	1.20	0.88	1.65	0.253	1.33	0.83	2.13	0.234
Dep3	1.32	0.96	1.83	0.091	1.61	1.01	2.57	0.043
Dep4	1.49	1.09	2.04	0.012	1.50	0.95	2.37	0.081
Dep5: Deprived	2.17	1.60	2.94	<0.001	1.51	0.92	2.47	0.105
Routine admission	1.00				-			
Emergency admission	2.58	2.10	3.17	<0.001	-			
Not seen in a specialist department	1.00				1.00			
Seen in a specialist department	0.46	0.33	0.62	<0.001	0.53	0.39	0.72	<0.001
Treated at a regional RT centre	1.00				1.00			
Treated at a high-workload hospital	0.71	0.55	0.92	<0.01	0.79	0.52	1.21	0.279
Treated at med-high workload hospital	0.71	0.53	0.94	0.016	0.62	0.42	0.92	0.016
Treated at med-low workload hospital	0.66	0.49	0.90	0.010	1.11	0.70	1.76	0.665
Treated at a low-workload hospital	0.78	0.53	1.15	0.204	0.69	0.48	1.00	0.053
Less than two weeks' wait ³	-				1.00			
More than two weeks' wait ³	-				0.64	0.44	0.93	0.021
Unknown or no treatment received	-				2.68	1.82	3.96	<0.001

¹ Age is also included in this model but the results not displayed

² Consultant workload was also significant but is excluded because only those with no consultant details had different survival than the rest.

³ Time between diagnosis and definitive treatment

Table 7.9 continued.

Model Variables included in the model	BLADDER				KIDNEY			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 3: Presentation variables¹								
Dep1: Affluent	1.00				1.00			
Dep2	1.13	0.82	1.55	0.448	1.65	1.04	2.60	0.032
Dep3	1.16	0.85	1.60	0.350	1.77	1.11	2.80	0.016
Dep4	1.31	0.97	1.78	0.080	1.74	1.11	2.75	0.016
Dep5: Deprived	1.94	1.45	2.61	<0.001	1.69	1.06	2.70	0.028
<i>Bladder</i>								
Transitional cell (TC)	1.00				1.00			
Papillary TC	0.48	0.37	0.61	<0.001	0.75	0.48	1.17	0.203
Other specified	1.57	1.15	2.16	<0.01	1.35	0.85	2.14	0.200
Unknown	1.80	1.22	2.66	<0.01	1.59	1.03	2.46	0.036
<i>Kidney</i>								
Renal cell	1.00				1.00			
Clear cell	0.48	0.37	0.61	<0.001	0.75	0.48	1.17	0.203
Other specified	1.57	1.15	2.16	<0.01	1.35	0.85	2.14	0.200
Unknown	1.80	1.22	2.66	<0.01	1.59	1.03	2.46	0.036
<i>Bladder</i>								
Grade 1	1.00				1.00			
Grade 2	1.73	1.13	2.66	0.012	-			
Grade 3-4	2.39	2.27	5.06	<0.001	4.92	2.69	8.99	<0.001
Unknown	2.65	1.71	4.11	<0.001	4.03	2.35	6.94	<0.001
<i>Kidney</i>								
Grade 1-2	1.00				1.00			
Grade 3-4	2.39	2.27	5.06	<0.001	4.92	2.69	8.99	<0.001
Unknown	2.65	1.71	4.11	<0.001	4.03	2.35	6.94	<0.001
Model 4: Treatment variables¹								
Dep1: Affluent	1.00				1.00			
Dep2	1.08	0.79	1.48	0.637	1.65	1.03	2.64	0.038
Dep3	1.01	0.74	1.39	0.941	1.65	1.03	2.66	0.038
Dep4	1.15	0.84	1.56	0.389	1.53	0.96	2.44	0.073
Dep5: Deprived	1.61	1.20	2.17	<0.01	1.62	0.99	2.64	0.054
Curative treatment intent	1.00				1.00	1.00		
Palliative treatment intent	5.71	4.48	7.29	<0.001	5.39	3.29	8.82	<0.001
Unknown treatment intent	2.43	1.81	3.28	<0.001	4.47	2.60	7.69	<0.001
Surgery alone	1.00				1.00	1.00		
Radiotherapy alone	2.38	1.69	3.35	<0.001	5.50	3.32	9.13	<0.001
Surgery and radiotherapy	1.68	1.29	2.18	<0.001	2.18	1.16	4.11	0.016
Surgery and chemotherapy	0.87	0.56	1.38	0.561	2.30	0.31	17.34	0.419
Unknown treatment combination	2.02	1.35	3.03	<0.01	3.44	2.03	5.85	<0.001
No treatment	3.29	2.47	4.38	<0.001	4.06	2.67	6.19	<0.001

¹ Age is also included in this model but the results not displayed

In model 3, grade and histological type were both important prognostic indicators for bladder cancer, but because there were no differences in the proportion of patients presenting with different grade and histological type of tumour, this did not explain the gradient in the deprivation-specific relative risks of death. For kidney cancer, grade and histological type were also important prognostic indicators. Deprived patients were more likely to present with renal cell tumours which appear to have a worse prognosis than clear cell tumours, and to present with tumours of unspecified cell type which had the worst prognosis. These differences account for the slight reduction in the relative risk of death between affluent and deprived (from 1.87 to 1.69; $p=0.028$).

Table 7.10: Patients diagnosed with bladder and kidney cancer in Scotland in 1997: multivariate influence of all the significant factors on the relative risk of death among deprived compared to affluent patients (Cox proportional hazards regression analysis)

Model Variables included in the model	BLADDER				KIDNEY			
	Relative risk	95% CI		P-value	Relative risk	95% CI		P-value
		Low	High			Low	High	
Model 5: Final model								
Dep1: Affluent	1.00				1.00			
Dep2	1.12	0.81	1.55	0.484	1.78	1.10	2.89	0.020
Dep3	1.07	0.77	1.48	0.703	1.58	0.97	2.57	0.066
Dep4	1.27	0.93	1.74	0.140	1.56	0.97	2.50	0.064
Dep5: Deprived	1.82	1.34	2.47	<0.001	1.58	0.95	2.61	0.078
Bladder								
Ages 30-49	1.00				1.00			
Ages 50-59	1.21	0.48	3.06	0.681	1.19	0.64	2.24	0.582
Ages 60-69	1.91	0.83	4.41	0.130	1.90	1.01	3.57	0.045
Ages 70-79	2.43	1.07	5.56	0.035	1.55	0.77	3.13	0.218
Ages 80+	3.17	1.38	7.27	<0.01	1.47	0.72	2.98	0.289
Kidney								
Ages 00-49	1.00				1.00			
Ages 50-64	1.21	0.48	3.06	0.681	1.19	0.64	2.24	0.582
Ages 65-74	1.91	0.83	4.41	0.130	1.90	1.01	3.57	0.045
Ages 75-79	2.43	1.07	5.56	0.035	1.55	0.77	3.13	0.218
Ages 80+	3.17	1.38	7.27	<0.01	1.47	0.72	2.98	0.289
No bed-days	1.00				1.00			
1-4 bed-days	1.08	0.79	1.46	0.629	0.86	0.55	1.37	0.532
5-10 bed-days	1.12	0.81	1.56	0.490	1.61	1.04	2.50	0.032
11+ bed-days	1.67	1.25	2.22	<0.001	1.44	0.99	2.11	0.056
Routine admission	1.00				-			
Emergency admission	1.43	1.13	1.82	<0.01	-			
Unknown admission type	0.50	0.15	1.67	0.263	-			
Not seen in a specialist department	1.00				1.00			
Seen in a specialist department	0.53	0.39	0.72	<0.001	0.74	0.54	1.02	0.063
Treated in regional RT centre	-				1.00			
Treated in high-workload hospital	-				2.10	1.28	3.43	<0.01
Treated in med-high workload hospital	-				1.04	0.66	1.65	0.858
Treated in med-low workload hospital	-				2.63	1.57	4.38	<0.001
Treated in low-workload hospital	-				1.36	0.89	2.08	0.158
Not treated in hospital	-				2.48	0.55	11.22	0.238
Bladder								
Transitional cell (TC)	1.00				-			
Papillary TC	0.62	0.48	0.81	<0.001	-			
Other specified	1.34	0.97	1.85	0.073	-			
Unknown	0.89	0.59	1.36	0.600	-			
Kidney								
Renal cell	1.00				-			
Clear cell	0.62	0.48	0.81	<0.001	-			
Other specified	1.34	0.97	1.85	0.073	-			
Unknown	0.89	0.59	1.36	0.600	-			
Bladder								
Grade 1	0.46	0.30	0.71	<0.001	1.00			
Grade 2	0.73	0.55	0.97	0.027	-			
Grade 3-4	1.00				2.04	1.06	3.95	0.034
Unknown	0.75	0.56	1.00	0.053	0.83	0.45	1.55	0.562
Kidney								
Grade 1-2	0.46	0.30	0.71	<0.001	1.00			
-	0.73	0.55	0.97	0.027	-			
Grade 3-4	1.00				2.04	1.06	3.95	0.034
Unknown	0.75	0.56	1.00	0.053	0.83	0.45	1.55	0.562
Curative treatment intent	1.00				1.00			
Palliative treatment intent	4.64	3.60	5.97	<0.001	5.27	3.17	8.75	<0.001
Unknown treatment intent	2.13	1.57	2.89	<0.001	4.99	2.77	8.98	<0.001
Surgery alone	1.00				1.00			
Radiotherapy alone	2.44	1.76	3.40	<0.001	10.41	5.74	18.90	<0.001
Surgery and radiotherapy	1.64	1.15	2.34	<0.01	2.85	1.48	5.48	<0.01
Surgery and chemotherapy	1.27	0.95	1.68	0.102	4.40	0.57	34.16	0.156
Unknown treatment combination	0.97	0.61	1.53	0.892	3.93	2.24	6.89	<0.001
No treatment received	1.42	0.93	2.15	0.102	5.04	3.10	8.20	<0.001

The treatment-related factors are considered in model 4, and treatment intent (curative or palliative) and the specific treatment combination given were both important prognostic factors. For bladder cancer, patients receiving surgery alone or in combination with chemotherapy had a better prognosis than patients receiving other treatment combinations or no treatment. However, information on treatment did not explain the deprivation-specific differences in relative risk of death. For kidney cancer, patients receiving surgery alone had the best prognosis, and after accounting for treatment received and the treatment intent, around a third of the difference in relative risk of death between affluent and deprived patients was explained (RR reduced from 1.87 to 1.62; $p=0.054$). The treatment given probably reflects the stage of the tumour, and so these differences may be a surrogate for stage.

Finally, all the significant factors from the grouped models were combined in a multivariate model (Table 7.10). After adjusting for all the factors that had a significant influence on survival the relative risk of death in deprived compared to affluent patients was increased for bladder cancer patients (from 1.67 to 1.82) and reduced by around a third for kidney cancer patients (from 1.87 to 1.58; $p=0.078$). For kidney cancer, the time from diagnosis to treatment factor was no longer significant in a model containing details of the specific treatment given.

Discussion

Deprived patients with bladder and kidney cancer were less likely than affluent patients to be treated in a regional RT centre or other high-workload hospital, despite guidelines recommending that all patients be referred to large hospitals with the necessary facilities. Patients receiving surgery alone had a better prognosis than those receiving other or combination treatments, probably reflecting differences in stage at diagnosis, and deprived patients were significantly less likely to receive surgery alone indicating a worse stage at diagnosis. They were also less likely to receive any treatment and more likely to receive treatment with palliative intent, again pointing to worse prognosis tumours. However, they were also less likely to attend a specialist department within three months of diagnosis, which may reflect lack of access to multidisciplinary teams to ensure the appropriateness of treatment. Deprived patients with bladder cancer were more likely to have comorbidity at diagnosis.

Deprivation-specific differences in outcome for bladder cancer patients do not appear to be explained by the factors relating to the patient, tumour, health care system and treatment studied in this chapter. It is surprising that of all the factors investigated, of which many proved to be of prognostic significance, none explained any of the differences between the deprivation groups. Indeed, the relative risk of death between affluent and deprived patients was increased with every single factor investigated with the exception of treatment which had virtually no effect on the relative risk (Table 7.8).

A study of bladder cancer patients in South Thames also looked at the relationship between hospital, treatment and tumour factors, and survival. They found that case severity was the most important influence on survival, and it influenced length of delay before treatment, grade and specialty of the surgeon, and main treatment allocation. After adjusting for case severity, variations in these processes of care were not strongly associated with variations in survival²²⁷. The differences in the Scottish data may also be explained by case severity, which could not be measured, but none of the factors that could be measured seemed to act as a surrogate to stage, in contrast to the South Thames study.

Survival would appear better for affluent than deprived patients if they were more likely to have investigations leading to more superficial tumours being recorded as invasive. However, it is unlikely that there is a bias in coding of bladder cancer by deprivation group, because incidence of bladder cancer is actually higher in the deprived group for patients diagnosed in 1997 (Figure 7.6). Deprived patients may be expected to have higher incidence of bladder cancer because smoking is a risk factor, so although this recording bias does not seem very plausible, it cannot be ruled out.

In contrast to bladder cancer, around 40% of the deprivation-specific gradient for kidney cancer patients was explained by differences in treatment. Survival was similar across the deprivation groups for patients who received no surgery, which will comprise largely of patients with advanced disease. For surgically-treated patients, the proportion treated with curative intent was similar across the deprivation groups but survival was lower for deprived compared to affluent patients. This could be an indication of worse stage of disease at presentation, or it could be a real effect. It is most likely a combination of both. Deprived patients were less likely to be treated in a high-workload hospital or attend a specialist

department, so they may not have been receiving the most effective and timely treatment. Without information on stage of disease, these questions cannot be answered.

In conclusion, there are very few studies in the literature looking at deprivation-specific differences in survival from bladder and kidney cancer. In this chapter, none of the factors investigated explained the differences in survival for bladder cancer. Routine data are clearly not sufficient to investigate the differences, and further investigation with data including stage is needed. However, it may not be possible to collect stage data of adequate quality routinely for bladder cancers^{22a}; a dedicated prospective audit may be necessary.

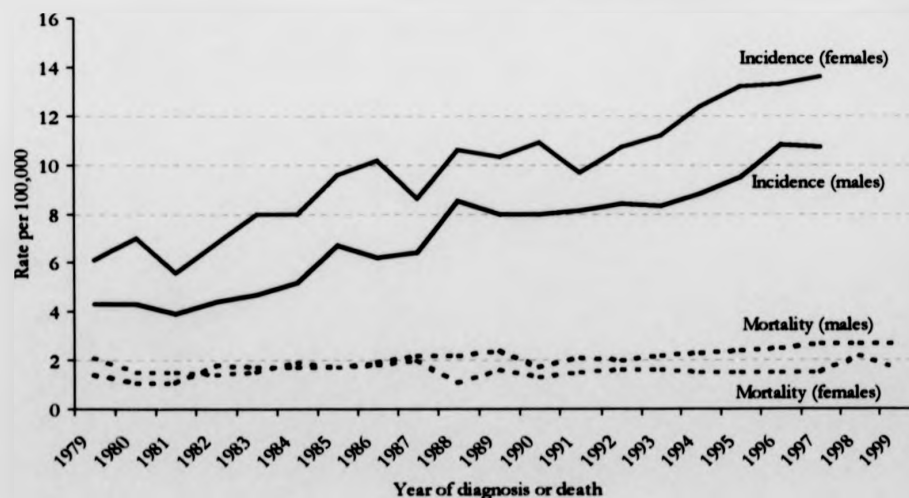
The kidney cancer analyses were based on a small sample of only 486 patients, so any interpretation of the results must be made with caution. Some of the differences between affluent and deprived patients were explained by differences in the treatment received. This may reflect a worse stage at diagnosis, but the data suggest that some of the differences are due to inequity in the access to health care services. It seems clear that if all patients with kidney cancer had equal access to multi-disciplinary teams in hospitals with all the necessary facilities for optimal treatment, the deprivation-specific gradient in risk of death from kidney cancer would be reduced.

MELANOMA OF THE SKIN

Background

Melanomas occur at a number of sites, however only cutaneous malignant melanomas of the skin (ICD10 code C43) are considered in this chapter and are referred to simply as melanoma. Melanoma is the 12th most common cancer among men (1.7% of all cancers) and the 10th most common cancer among women (2.7%) in Scotland. A total of 673 new cases were diagnosed in 1997. Incidence has doubled over the last 20 years, and is continuing to increase rapidly in both sexes (Figure 8.1).

Figure 8.1: Melanoma of the skin in Scotland: trends in incidence (1979-97) and mortality (1979-99), all ages (European age-standardised rates)

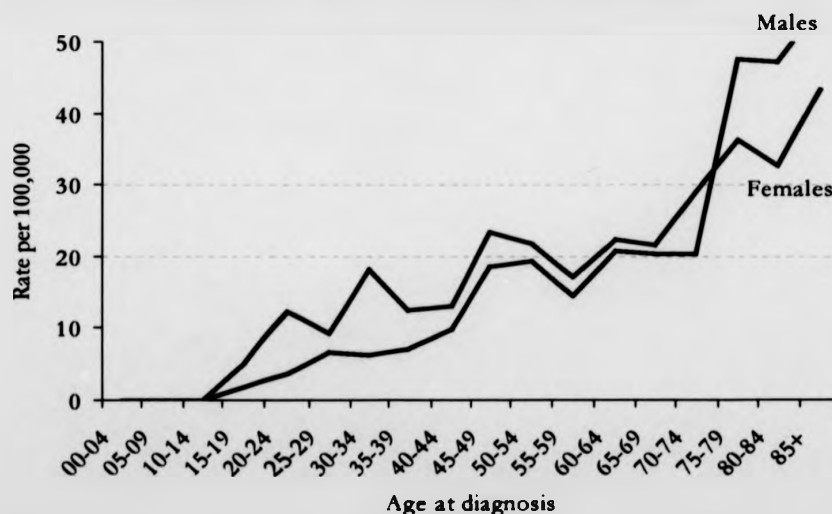


Similar increases in melanoma incidence reported elsewhere are not thought to be due to changes in diagnostic criteria²²⁰, and the Scottish Melanoma Group have stated there has

been no change in pathological diagnostic criteria in Scotland over the time period¹¹¹. Completeness of ascertainment of cases is verified against a specialist Scottish melanoma register which has been running since 1979 so changes in reporting are also an unlikely explanation for the increase.

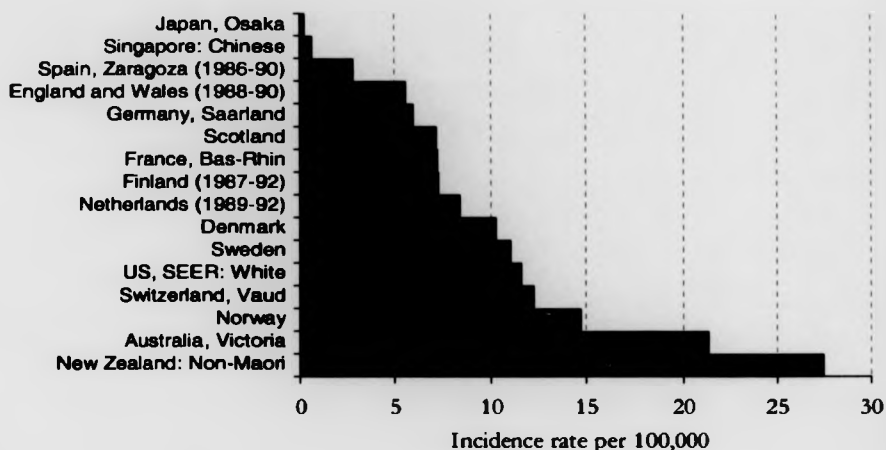
Melanoma is one of the few cancers that are common in both young men and women. Incidence is higher in women than men at all ages except the very elderly (aged 80 and over; Figure 8.2). Incidence has been increasing in all age groups, and the increase has been particularly marked for males aged 80 and over. An overview of trends in incidence, mortality and survival in Scotland from 1979-94¹¹¹ found that incidence of melanoma in younger women (aged under 65) had stabilised, but this was not observed in the current data for Scotland.

Figure 8.2: Age-specific incidence of melanoma in Scotland during 1997, by sex



Over the last 40 years, the incidence of melanoma has risen steadily worldwide, with the highest rates in New Zealand and Australia and the lowest in parts of Asia. Incidence in Scotland is relatively low (Figure 8.3), and as two-thirds of all melanomas can be attributed to solar radiation²³⁰, this is probably due to the local climate.

Figure 8.3: International comparison of melanoma incidence, around 1988-92 (world standardised rates)



Source: Cancer Incidence in Five Continents, Vol. VII⁸⁸

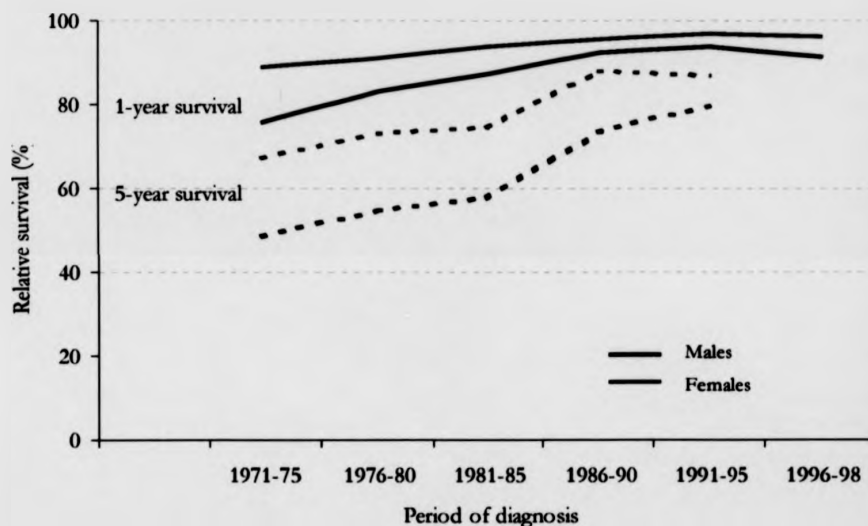
Although mortality from melanoma appears relatively unchanged since around 1980 (Figure 8.1), these age-standardised rates mask an increasing trend in the older age groups. A reduction in mortality in younger women has been noted in Europe²³¹, England and Wales²³² and Scotland¹¹¹, and although a downward trend is not evident from recent Scottish data, the mortality rates appear to be fairly constant in the younger women.

Projections of recent trends in incidence and mortality in Scotland¹⁵² suggest a further large increase in melanoma incidence in the decade up to 2010-14, with up to 75% more cases a year expected. Mortality rates are expected to remain unchanged.

For patients diagnosed with melanoma in Scotland in 1971-75, survival at five-years after diagnosis was significantly higher in females (67%) than males (49%). Since then survival has improved steadily in both sexes and although it is still higher in females, the gap between the sexes has reduced substantially with five-year survival for patients diagnosed in 1991-95 of 87% for females and 80% for males (Figure 8.4). Similar trends have been observed in England and Wales⁴. In Scotland the survival rates appear to be levelling off in the most recent data of patients diagnosed during 1996-97. The prevailing differences between the

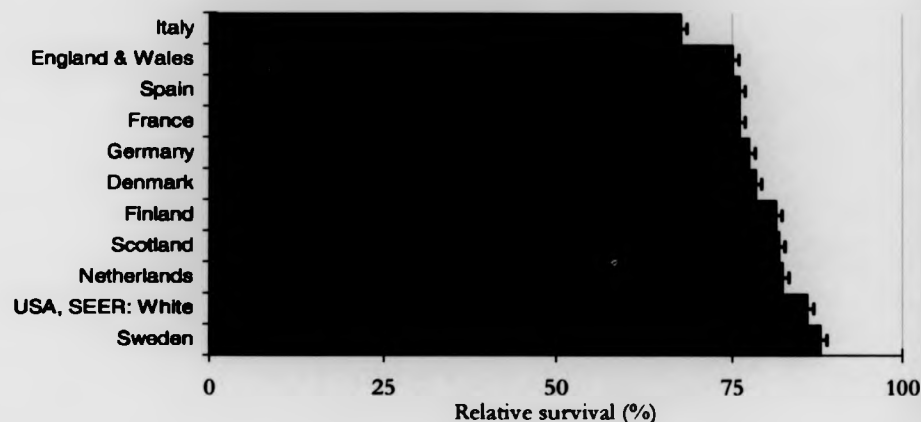
sexes are probably due to biological behaviour or diagnostic delay²³³, and stage at diagnosis²³⁴. In a study by the Scottish Melanoma Group, improvements in survival during the mid-1980s were attributed to patients presenting earlier with thinner tumours, but a continuing improvement in the late-1980s could not be accounted for by a fall in average tumour thickness¹¹¹.

Figure 8.4: Patients diagnosed with melanoma in Scotland during 1971-1997: trends in relative survival by sex



Unlike most cancers, survival from melanoma in Scotland is among the highest when compared to other countries in Europe and to the USA (Figure 8.5). Several factors have been linked to prognosis of patients with melanoma, the most important being thickness of the lesion, number of involved nodes and metastatic status. Site of the lesion on the body, sex and age have also been shown to have prognostic value²³⁵. That survival in Scotland compares favourably to survival elsewhere may be, in part, due to a successful public education campaign in the mid-1980s in Scotland aimed at encouraging earlier diagnosis²³⁶. As mortality has not declined substantially, an alternative explanation could be lead time or length bias²³⁷.

Figure 8.5: Melanoma of the skin: international comparison of five-year relative survival (with 95% confidence intervals), selected countries, patients diagnosed around 1985-89, all ages¹



Sources: Berrino *et al.*⁶, Gatta *et al.*¹³⁹, Coleman *et al.*⁴

¹ Women diagnosed 1986-90, aged 15-99 in England & Wales; women aged 15-99 in Scotland

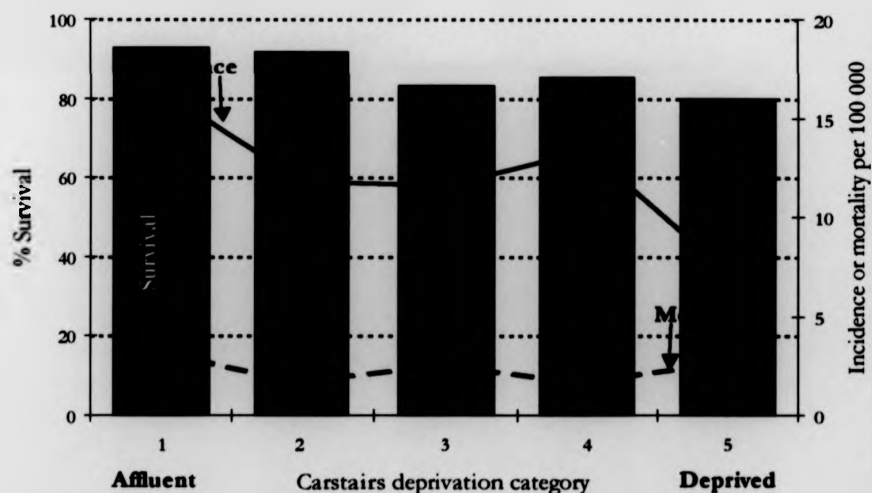
In this chapter the survival of 673 patients diagnosed with melanoma in Scotland in 1997 is investigated to identify reasons for differences in survival by deprivation category. For definitions of the variables included in the analyses, please refer to Chapter 2.

Results and commentary

For patients diagnosed in Scotland in 1997, incidence was twice as high in people from the most affluent areas (16.4 per 100 000) as in those from the most deprived areas (7.2). The mortality rates (for patients dying in 1999) show very little variation across deprivation groups. There was a very large difference in two-year survival ranging from 91% for affluent compared to 72% for deprived patients. This translates into an almost three-fold risk of death within two years of diagnosis for deprived compared to affluent patients. This large survival differential explains why the deprivation-specific trend in incidence is not matched by a similar trend in mortality (Figure 8.6).

Higher incidence and survival for affluent compared to deprived patients has previously been shown in a number of studies^{234,238,239}. The higher incidence in affluent groups may be related to sun exposure on holidays in hot climates²⁴⁰, and if this is the case, the incidence differential will be reduced in the future mirroring the increase in economical holidays abroad. If incidence in deprived groups does increase in line with affluent groups, the difference in survival between affluent and deprived will have even larger public health implications. Affluent patients presenting more frequently with thinner lesions may explain the higher survival in the affluent group. However, another study by the Scottish Melanoma Group found that differences in survival by socio-economic group were not fully accounted for by tumour thickness, ulceration, age or body site of tumour²⁴⁶.

Figure 8.8: Patients diagnosed with melanoma in Scotland in 1997: incidence¹ and two-year relative survival², and mortality¹ in 1999, by deprivation category



¹ Age-standardised rates per 100,000 person-years at risk (European standard population)

² Using deprivation-specific life tables; adjusted for sex

Of the 673 patients diagnosed in 1997, 183 (27%) were from the affluent group and only 74 (11%) from the deprived group (Table 8.1). Melanoma was more common in females (60%) than males, and the distribution of age of diagnosis was lower than for most cancers, with a median age of 56 years and an inter-quartile range from 41 to 73 years.

Table 8.1: Patients diagnosed with melanoma in Scotland during 1997: demographic data by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	No. of females	Median age (inter-quartile range)	Cases for which:				No. of urban residents ¹
				First primary	Simultaneous primary	Previous primary at same site	Previous primary elsewhere	
Affluent	183 (27%)	109 (60%)	54 (42-73)	177 (97%)	1 (1%)	0 (0%)	5 (3%)	88 (48%)
2	160 (24%)	99 (62%)	54 (41-73)	149 (93%)	0 (0%)	1 (1%)	10 (6%)	44 (28%)
3	119 (18%)	73 (61%)	58 (45-71)	102 (86%)	0 (0%)	0 (0%)	17 (14%)	42 (35%)
4	137 (20%)	79 (58%)	56 (36-70)	129 (94%)	1 (1%)	0 (0%)	7 (5%)	66 (48%)
Deprived	74 (11%)	46 (62%)	59 (44-76)	69 (93%)	0 (0%)	0 (0%)	5 (7%)	64 (86%)
Total	673 (100%)	406 (60%)	56 (41-73)	626 (93%)	2 (0%)	1 (0%)	44 (7%)	304 (45%)

¹ Chi-square test for association: $p < 0.001$

There was no significant difference in sex distribution between the deprivation groups, but deprived patients were more likely to be older at presentation (30% aged 75 or over compared to 18% of affluent patients). There was no trend in age distribution across the deprivation groups ($p=0.428$).

Melanoma was the first primary malignancy for most patients (93%). The proportion of patients with a previous primary varied between the deprivation groups but without a clear trend. Deprived areas in Scotland are largely urban; therefore, deprived patients with melanoma were more likely to come from urban areas (86% compared to 48% of affluent patients).

Organisation of services

There is increasing public awareness of the potential dangers of changes in the size, shape or colour of moles on the skin. Information should be available for GPs on sending patients with suspected melanoma to rapid referral clinics¹⁰³. Such clinics aim to see patients within two weeks of referral, and should have facilities for immediate biopsy if the likelihood of melanoma is considered high. Prompt pathological confirmation of the diagnosis is needed to assess the tumour thickness. Once the diagnosis is confirmed further surgery may be required and the patient should have access to this within 2-4 weeks of the first surgical episode¹⁰².

For patients diagnosed with melanoma in Scotland in 1997, 40% attended a regional RT centre at some point during their cancer spell (Table 8.2). Surgery was performed at a high-workload hospital (treating at least 20 melanoma patients per year) for 56% patients; 22% were treated at a regional RT centre and 34% at other high-workload hospitals. A further 26% of patients attended only medium-low or low-workload hospitals. The proportion of patients treated at a high-workload hospital varied by deprivation group, favouring affluent patients (67% affluent compared to 54% deprived; $p=0.011$).

In Scotland, many melanoma patients are treated as day cases without an inpatient visit, so using the hospital discharge information (SMR01) to look at consultant workload and specialty of the department of surgery gives a very incomplete picture of care. Overall, 54% of patients did not have an SMR01 record at the time of their surgery and most of these patients were probably treated as an outpatient.

Table 8.2: Patients diagnosed with melanoma in Scotland during 1997: access to health care by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Attended a regional RT centre ¹	Attended a specialist department ²	Main treatment at a regional RT centre ³	Treated in a high-workload hospital ⁴	Seen by a high-workload consultant ⁵	Emergency admission	More than two weeks' delay between diagnosis and treatment ⁶
Affluent	183	97 (53%)	136 (74%)	57 (31%)	122 (67%)	64 (45%)	8 (4%)	51 (28%)
2	160	52 (33%)	121 (76%)	28 (18%)	85 (53%)	42 (33%)	7 (4%)	59 (37%)
3	119	45 (38%)	90 (76%)	27 (23%)	56 (47%)	27 (29%)	4 (3%)	36 (31%)
4	137	52 (38%)	102 (74%)	21 (15%)	76 (55%)	44 (40%)	5 (4%)	45 (33%)
Deprived	74	25 (34%)	43 (58%)	15 (20%)	40 (54%)	22 (42%)	11 (15%)	30 (42%)
Total	673	271 (40%)	492 (73%)	148 (22%)	379 (56%)	199 (38%)	35 (5%)	221 (33%)
Significance ⁷		$p<0.001$	$p=0.242$	$P<0.01$	$p=0.011$	$p=0.293$	$p=0.010$	$p=0.284$

¹ Within 6 months of diagnosis

² Within 3 months of diagnosis

³ Number of patients whose surgery was performed at a regional centre with RT provision

⁴ Number of patients whose surgery was performed in a hospital seeing at least 23 melanoma patients per year (highest workload quartile)

⁵ Consultant seeing at least 20 melanoma patients per year (highest workload quartile); percentage of those with SMR01 consultant details

⁶ Days between diagnosis and definitive treatment; percentage of those with a definitive treatment date

⁷ Chi-square test for association

Deprived patients were slightly more likely to be treated as an outpatient (57% compared to 53% of affluent patients). Overall, of those treated as an inpatient (46%), 2% were treated in a dermatology department, 29% in a plastic surgery department and 15% in general surgery. Deprived patients were significantly more likely to be treated in a plastic surgery department (75% compared to 65% of affluent patients; $p=0.040$).

The distribution of affluent and deprived patients varies substantially by health board as do the melanoma services available. Differences by deprivation group in the proportion of patients treated as an outpatient and the proportion treated in different surgical specialities are partly reflected by the services available in different areas. For example, in Lothian, 69% of patients were treated as outpatients compared to 56% of Greater Glasgow patients and only 29% of Grampian patients. In Tayside, a high proportion of patients (51%) were treated by plastic surgeons compared to 16% of Lothian patients and none of the Highlands and Islands patients.

Of patients treated as an inpatient, 38% were managed by a high-workload consultant (seeing at least 20 melanoma patients per year), and this did not vary between the deprivation groups.

Delay

For a third of patients, at least two weeks elapsed between diagnosis and surgery (Table 8.2), and the wait was greater than 1 month for 21% of patients. Deprived patients were more likely to have a delay of at least two weeks (42% compared to 28% of affluent patients), although again, there was no clear trend across the deprivation groups. Patients with lesions on the face, head and neck were most likely to have a delay (43% compared to 33% overall); specifically, patients with lentigo maligna tumours had the longest wait (53% waited more than two weeks for surgery). Patients with superficial spreading tumours had the shortest wait (only 29% waited more than two weeks for surgery).

Emergency admissions were relatively rare for melanoma (5%; Table 8.2) although still higher than might be expected. Deprived patients were significantly more likely to present as an emergency than patients in the other deprivation groups (15%; $p=0.010$).

Mode of presentation

The signs of early melanoma include change in size, shape or colour of an existing melanocytic naevus, or development of a new brown or black pigmented lesion in an adult. In the great majority of cases of suspected melanoma the first appropriate investigation is an excision biopsy and histopathological examination to determine the most important features of the tumour including tumour thickness, level of invasion and clearance margins. The majority of patients present with early stage melanoma and do not have clinical lymphadenopathy or evidence of distant spread. For patients with thin lesions (less than 1mm thick), no additional investigations are currently considered necessary other than a careful examination of the skin for a second primary tumour and for atypical or dysplastic naevi. Melanoma patients are generally followed up by hospital specialists at three-monthly intervals for a minimum of three years, and five years for patients with thicker tumours²⁴¹.

Unfortunately, no information on tumour thickness, level of invasion or clearance margins is recorded on SOCRATES. The Scottish Melanoma Group collects this information but it was not available for the analyses in this chapter. The only factors relating to the tumour that can be investigated are the body site and histological type.

Overall, the most common body site for melanoma was the lower limb (Table 8.3); however as noted previously²³⁹, tumours on the trunk are more common for males. For patients diagnosed with melanoma in Scotland in 1997, 33% of the tumours in males were on the trunk compared to 14% for females, and 46% of the tumours in females were on the lower limb compared to 21% for males. A higher proportion of males than females had tumours on the head, neck or face (28% compared to 19%). Tumours on the trunk were less common for deprived than affluent patients, and tumours on the lower limb and head, face and neck were more common in deprived than affluent patients. In particular, deprived women had a higher proportion of head, neck and face tumours than affluent women (20% compared to 12%) and a lower proportion of lesions on the upper limb (13% compared to 22%); deprived men had a lower proportion of trunk lesions than affluent men (21% compared to 34%). Site of lesion on the body was also related to age, with lesions on the head, neck and face more common in elderly patients (56% of patients aged 80 and over compared to 12% of patients aged under 50).

Table 8.3: Patients diagnosed with melanoma in Scotland during 1997: body site and histological type by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Site ¹					Type ¹				
		Head, face and neck	Trunk	Lower limb	Upper limb	Unknown	Superficial spreading	Lentigo maligna	Nodular	Acral	Other and unspecified
Affluent	183	36 (20%)	43 (24%)	67 (37%)	34 (19%)	3 (2%)	97 (73%)	13 (10%)	13 (10%)	9 (7%)	51 (28%)
2	160	31 (20%)	37 (23%)	57 (36%)	33 (21%)	2 (1%)	90 (82%)	12 (11%)	4 (4%)	4 (4%)	50 (31%)
3	119	32 (28%)	27 (24%)	37 (32%)	18 (16%)	5 (4%)	53 (77%)	5 (7%)	9 (13%)	2 (3%)	50 (42%)
4	137	33 (25%)	27 (20%)	51 (39%)	21 (16%)	5 (4%)	67 (73%)	8 (9%)	11 (12%)	6 (7%)	45 (33%)
Deprived	74	18 (26%)	12 (17%)	29 (42%)	10 (14%)	5 (7%)	38 (81%)	2 (4%)	5 (11%)	2 (4%)	27 (36%)
Total	673	150 (23%)	146 (22%)	241 (37%)	116 (18%)	20 (3%)	345 (77%)	40 (9%)	42 (9%)	23 (5%)	223 (33%)
Significance		$p=0.802^2$				$p=0.121^1$	$p=0.548^2$				$p=0.127^1$

¹ Percentage of patients with a known category, except 'unknown', presented as a percentage of the total

² Significance of association between deprivation category and percentage of patients in each category excluding those in the unknown category

³ Significance of proportion unknown across the deprivation categories

Diagnosis was microscopically verified for all patients. However, the histological type of the tumour was unspecified for 33% of patients (Table 8.3). For patients with known histological type, 77% were superficial spreading tumours, 9% lentigo maligna, 9% nodular and 5% acral. Women were significantly more likely to have superficial spreading tumours (82% compared to 68% of males) and less likely to have nodular tumours (6% compared to 15%). The same pattern was seen for young and old patients. There were no differences in histological type between the deprivation groups.

Body site and histological type are related. Acral tumours occur on the soles and palms, and were therefore contained within the upper and lower limb sites (100%). These are tumours with a high risk of recurrence. Lentigo maligna tumours occurred predominantly on the face (88%).

Patients with lesions on the head, face or neck were the most likely to attend the plastic surgery department, and to be treated as an inpatient (Table 8.4). Over half of patients with lentigo maligna or acral tumours were referred to the plastic surgery unit. Patients with superficial tumours were more likely to be treated as outpatients, although this varied substantially by health board of residence.

Table 8.4: Patients diagnosed with melanoma in Scotland during 1997: body site and histological type by surgical department (number and percentage of cases)

Site and type	Surgical department			
	Dermatology	General surgery	Plastic surgery	No inpatient visit recorded
Site¹				
Head, face or neck	2 (1%)	14 (9%)	76 (51%)	58 (39%)
Trunk	4 (3%)	17 (12%)	32 (22%)	93 (64%)
Lower limb	3 (1%)	48 (20%)	66 (28%)	124 (51%)
Upper limb	4 (3%)	21 (18%)	21 (18%)	70 (60%)
Unknown	0 (0%)	2 (10%)	2 (10%)	16 (80%)
Type²				
Superficial	11 (3%)	46 (13%)	83 (24%)	205 (59%)
Lentigo maligna	0 (0%)	4 (10%)	22 (55%)	14 (35%)
Nodular	0 (0%)	11 (26%)	12 (29%)	19 (45%)
Acral	0 (0%)	5 (22%)	12 (52%)	6 (26%)
Other and unknown	2 (1%)	36 (16%)	68 (30%)	117 (52%)
Total	13 (2%)	102 (15%)	197 (29%)	361 (54%)

¹ Chi-square test for association: $p < 0.001$

² Chi-square test for association: $p < 0.001$

Acral tumours, which are difficult to excise completely, were largely (82%) treated in the regional RT centres and other high-workload hospitals (Table 8.5). Tumours on the head, face and neck were also more often treated in regional RT centres or other high-workload hospitals than tumours on other sites of the body.

Table 8.5: Patients diagnosed with melanoma in Scotland during 1997: body site and histological type by hospital workload (number and percentage of cases)

Site and type	Hospital of surgery					
	Regional RT centre	High-workload hospital	Medium-high workload hospital	Medium-low workload hospital	Low-workload hospital	No hospital details
Site¹						
Head/face/neck	27 (18%)	72 (48%)	12 (8%)	10 (7%)	24 (16%)	5 (3%)
Trunk	30 (21%)	42 (29%)	27 (18%)	16 (11%)	20 (14%)	11 (8%)
Lower limb	25 (22%)	34 (29%)	17 (15%)	12 (10%)	20 (17%)	8 (7%)
Upper limb	59 (24%)	81 (34%)	17 (7%)	34 (14%)	31 (13%)	19 (8%)
Unknown	7 (35%)	2 (10%)	1 (5%)	5 (25%)	4 (20%)	1 (5%)
Type²						
Superficial	61 (18%)	122 (35%)	48 (14%)	46 (13%)	43 (12%)	25 (7%)
Lentigo maligna	5 (13%)	21 (53%)	4 (10%)	3 (8%)	7 (18%)	0 (0%)
Nodular	7 (17%)	10 (24%)	5 (12%)	8 (19%)	9 (21%)	3 (7%)
Acral	9 (39%)	10 (43%)	0 (0%)	1 (4%)	1 (4%)	2 (9%)
Other and unknown	66 (30%)	68 (30%)	17 (8%)	19 (9%)	39 (17%)	14 (6%)
Total	148 (22%)	231 (34%)	74 (11%)	77 (11%)	99 (15%)	44 (7%)

¹ Chi-square test for association: $p < 0.01$

² Chi-square test for association: $p < 0.001$

Comorbidity

Overall, 17% of patients had spent more than 10 days in hospital during the two years prior to diagnosis. Comorbidity was lower when measured by the disease-based measures (Charlson or Scottish indices). For all three comorbidity measures, deprived patients had much higher comorbidity at the time of cancer diagnosis. With the bed-days score, comorbidity in deprived patients was double that in affluent patients (27% compared to 14%; Table 8.6). Comorbidity was also strongly related to age, for example, 17% of patients aged 80 and over had comorbidity as measured by the Charlson score, compared to none aged less than 50 years (data not shown).

Table 8.6: Patients diagnosed with melanoma skin cancer in Scotland during 1997: comorbidity by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Comorbidity		
		Bed-days ¹	Scotland ²	Charlson ³
Affluent	183	26 (14%)	9 (5%)	2 (1%)
2	160	19 (12%)	11 (7%)	6 (4%)
3	119	24 (20%)	7 (6%)	11 (9%)
4	137	25 (18%)	11 (8%)	6 (4%)
Deprived	74	20 (27%)	10 (14%)	8 (11%)
Total	673	114 (17%)	48 (7%)	33 (5%)
<i>Significance⁴</i>		<i>p<0.01</i>	<i>p=0.173</i>	<i>p<0.01</i>

¹ More than 10 inpatient bed-days in the two years prior to cancer diagnosis

² Any one of certain comorbid conditions recorded in the two years prior to one month after diagnosis (see Chapter 1)

³ Any one of certain comorbid conditions recorded in the five years prior to diagnosis (see Chapter 1)

⁴ Chi-square test for association

Treatment

Surgical excision of thin primary melanomas is currently the only curative therapy for melanoma. The exact margin of excision of normal skin around the tumour varies with tumour thickness, and the maximum margin currently considered necessary even for thick melanomas is 3cm of normal skin. The great majority of patients with early stage melanoma can be treated with local anaesthesia, but a small proportion require skin grafting which may involve an inpatient stay and general anaesthesia. Patients with stage 3 disease, where melanoma has spread to the local draining lymph nodes, require full surgical lymph node dissection, and patients with advanced disease may obtain palliative benefit from surgical debulking and reduction of the tumour load. Adjuvant radiotherapy and chemotherapy are not considered for early stage tumours. Patients with local-regional recurrence may be put forward for systemic adjuvant clinical trials, and some patients with metastatic tumour may also receive chemotherapy. No clinical trials have confirmed significant survival benefits from adjuvant chemotherapy. Radiotherapy may be offered to patients with advanced disease to relieve pain from bone metastases.

For patients diagnosed with melanoma in Scotland in 1997, 97% had their tumour excised surgically, and the surgical intent was recorded as curative for 92% of patients. Three percent received palliative radiotherapy and 1% chemotherapy. These proportions did not vary by deprivation group (Table 8.7).

Table 8.7: Patients diagnosed with melanoma skin cancer in Scotland during 1997: treatment received by deprivation category (number and percentage of cases)

Deprivation category	No. of patients	Surgery	Radiotherapy	Chemotherapy
Affluent	183	180 (98%)	5 (3%)	6 (3%)
2	160	159 (99%)	2 (1%)	2 (1%)
3	119	114 (96%)	5 (4%)	1 (1%)
4	137	133 (97%)	5 (4%)	1 (1%)
Deprived	74	72 (97%)	2 (3%)	0 (0%)
Total	673	658 (98%)	19 (3%)	10 (1%)
<i>Significance¹</i>		<i>p=0.424</i>	<i>p=0.642</i>	<i>p=0.197</i>

¹ Chi-square test for association

Two-year survival

Univariate analyses

Factors that had an influence on the differences in two-year survival between deprivation groups were investigated in Cox proportional hazards regression models. In the initial model containing deprivation only, the relative risk of death within two years of diagnosis was substantially raised for deprived compared to affluent patients with melanoma (RR=2.89 (95% CI: 1.36-6.15); $p<0.01$). This is a much larger excess risk than seen for the other cancers studied in this thesis, but based on a smaller sample of patients.

Patient characteristics

Survival was strongly related to age, with two-year survival decreasing with increasing age (97% for patients aged under 50, 91% for ages 50-69, 82% for ages 70-79, and 61% for those aged 80 or over). The Scottish Melanoma Group study of patients diagnosed during 1979-94 found that younger patients had thinner tumours but this only partly explained their better survival¹¹¹. For patients diagnosed in 1997, including age in the model significantly ($p<0.001$) improved the model fit. Age differences did not explain the deprivation-specific differences in survival: the relative risk of death in deprived compared to affluent patients was reduced from 2.89 to 2.54. The model containing deprivation and age was used as the null model, and each factor was added and then removed from the null model one at a time to test its significance as a prognostic factor for melanoma (Table 8.8).

Table 8.8: Patients diagnosed with melanoma in Scotland during 1997: univariate influence of individual factors on the relative risk of death within two years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analysis)

Variables included in the model ¹	Relative risk ²	95% CI		P-value ³	P-value of added term ⁴
		Low	High		
Initial model: Deprivation category	2.89	1.36	6.15	<0.01	
Patient characteristics:					
Age (null model) ⁵	2.54	1.18	5.43	0.017	<0.001
Sex	2.64	1.23	5.65	0.012	<0.001
Health board of residence	2.06	0.89	4.77	0.09	0.63
Urban indicator	2.40	1.10	5.24	0.028	0.54
Previous history of primary cancer	2.45	1.14	5.27	0.021	0.27
Bed-days comorbidity index	1.87	0.86	4.06	0.114	<0.001
Charlson comorbidity index	2.22	1.03	4.79	0.042	<0.01
Scottish comorbidity index	2.40	1.12	5.17	0.025	0.14
Health care factors:					
Attended a high-workload hospital?	2.93	1.36	6.31	<0.01	0.06
Workload of hospital of surgery	2.62	1.21	5.68	0.015	0.48
Specialty of department of surgery ⁶	2.61	1.21	5.62	0.014	0.68
Emergency admission ⁷	2.26	1.05	4.87	0.037	0.07
Time from diagnosis to surgery	2.59	1.20	5.57	0.015	<0.001
Consultant workload ⁸	2.78	1.28	6.01	0.010	0.012
Tumour characteristics⁹:					
Histological type	2.64	1.23	5.67	0.013	0.025
Site of lesion on the body	2.10	0.96	4.57	0.061	<0.001
Treatment factors:					
Treatment intent (curative or palliative)	2.85	1.32	6.15	<0.01	<0.001
Surgery (yes or no)	2.65	1.23	5.71	0.013	<0.001
Radiotherapy (yes or no)	2.43	1.13	5.24	0.023	<0.001
Chemotherapy (yes or no)	3.33	1.52	7.32	<0.01	<0.001

¹ Each categorical variable is added individually to the null model containing deprivation category and age

² Relative risk of death in the deprived compared to affluent group

³ Significance of the difference in the relative risk between affluent and deprived

⁴ Improvement in model fit when each categorical variable is added to the null model

⁵ The significance of the age term is tested against the initial model containing only deprivation category

⁶ Includes category "Unknown" for all patients not treated in the inpatient setting

⁷ Outpatients were all assumed to be routinely admitted

⁸ See Table 8.3 for histological type and body site groupings

In agreement with studies in the literature, survival was significantly higher for females than males (92% compared to 83%). This difference remained after adjusting for variations in age and site of lesion on the body, and may be accounted for by tumour stage²⁴², although this was not found to be the case in an audit of Yorkshire patients²³⁹. Adding sex to the null model improved the model fit but did not explain the differences in survival between the deprivation groups (RR reduced from 2.89 to 2.64). Survival did not vary significantly by

health board, and survival was similar for urban and rural residents. Adding these residential factors to the null model did not, therefore, improve the model fit. Survival was significantly lower for patients who had a previous primary cancer at any site (76% compared to 89%; $p < 0.01$), but this difference was accounted for by the older age of patients with a previous primary. Adding cancer history to the null model including deprivation and age, therefore, did not improve the model fit.

All three measures of comorbidity were independently and very strongly related to survival. Patients who had spent more than 10 days in hospital in the two years prior to the melanoma diagnosis had significantly poorer two-year survival than those with fewer or no days spent in hospital (54%, compared to 78% for 5-10 days and 93% for < 5 days; $p < 0.001$). Any comorbidity compared to no comorbidity was associated with reduced survival when measured with both the Charlson index (55% at two-years compared to 90%; $p < 0.001$) and the Scottish index (69% at two-years compared to 90%; $p < 0.001$). The bed-days and Charlson indices both improved the fit of the model compared to the null model; however, the Scottish index was no longer a significant factor after adjusting for age (Table 8.8). Differences in comorbidity measured by the bed-days index accounted for half the difference in risk of death between affluent and deprived patients reducing the relative risk from 2.89 to 1.87 and rendering the difference non-significant.

Health care factors

Patients attending a regional RT centre at some point during their cancer spell had significantly worse survival than patients attending other high-workload hospitals. This was because patients with worse prognosis were being referred to the regional RT centres for radiotherapy. If patients receiving radiotherapy are excluded from the analyses then there were no differences in survival by hospital group (data not shown). Patients who had their surgery completely outside the hospital setting had the highest survival (93%), presumably because these were patients with very small lesions excised by their GP. Patients who received their surgery at a regional RT centre had the lowest survival (84%); these differences in survival were not significant. There were no differences in survival by surgical department (dermatology, general medicine or plastic surgery), and those treated as inpatients had similar survival to those treated as outpatients. Adding workload of the hospital of surgery or specialty of the department of surgery to the null model did not improve the model fit (Table 8.8).

Patients who presented as an emergency admission had poorer survival (71%) than those admitted routinely (88%) or with treated as outpatients (89%; $p < 0.001$); however, inclusion of this factor in the null model did not improve the model fit. Survival was not influenced by length of time between diagnosis and surgery (less than or greater than two weeks). However, patients not assigned to a waiting time (i.e. those who had no surgery) had significantly poorer survival ($p < 0.001$). Inclusion of time from diagnosis to surgery in the null model improved the model fit but only as an indication of whether or not the patient received any surgery. Of patients treated as inpatients, those who were managed by a high-workload consultant (> 25 cases per year) at surgery had the highest survival (90%) but there was no trend across the other consultant workload groups. After adjusting for age, patients who were managed by a high-workload clinician had a relative risk of death of 0.38 compared to those managed by a low-workload clinician ($p = 0.076$). Inclusion of clinician workload in the null model improved the model fit but did not explain the deprivation-specific differences in survival (Table 8.8).

Tumour characteristics

Survival varied by histological type; with significantly lower two-year survival for patients with nodular tumours than other types (69% compared to 94% for superficial spreading, 90% for lentigo maligna, 83% for acral and 84% for other and unknown tumour types). Previous research had suggested that acral melanomas had the worst prognosis^{243,244} but evidence is conflicting²⁴⁵ and this is not supported by the analyses presented here. Site of the lesion on the body was also significantly related to survival, with poorer survival for patients with head, neck and face lesions compared to other locations (79% compared to 95% for upper limb, 92% for trunk and 91% for lower limb; $p < 0.001$). The twenty patients with lesions at other and unknown locations had significantly poorer survival (60%). The Scottish Melanoma Group study of patients diagnosed during 1979-94 found no difference in survival by body site or histological type once tumour thickness was controlled for¹¹¹. In the Yorkshire audit²³⁹ survival also varied significantly by body site, but again this difference disappeared when case-mix factors including tumour thickness were adjusted for in their model. For patients diagnosed in Scotland in 1997, body site explained around a quarter of the differences in risk of death between affluent and deprived patients, reducing it from 2.89 to 2.10 and rendering it marginally non-significant ($p = 0.06$). This may actually be an

underlying measure of tumour thickness. Histological type also improved the model fit, but only explained a small proportion of the deprivation-specific differences.

Treatment factors

Unsurprisingly, patients who were treated with curative intent had significantly higher two-year survival than those treated with palliative intent (93% compared to 39%). Survival was 77% for the small group (6%) of patients whose treatment intent was unknown. Most patients (87%) were treated with curative intent; 6% were treated with palliative intent. The small number of patients who did not receive surgery had significantly poorer survival than those who did receive surgery (36% compared to 90%). Patients who received chemotherapy or radiotherapy had a significantly lower survival than those who did not. Of those patients treated with palliative intent, a third received radiotherapy. Inclusion of treatment information improved the model fit but did not explain the deprivation-specific differences in survival (Table 8.8), as the relative risk of death for deprived compared to affluent patients was virtually unchanged from the null model.

Multivariate analyses

In the main multivariate analyses, the factors were grouped into patient characteristics, tumour characteristics, health care system factors and treatment factors (Table 8.9). Each factor was examined allowing for all related factors, and only factors that improved the model fit are presented (models 1-4). Deprivation group and age were included in each model. The significant factors in each of these group models were then included in the final model (Table 8.10; model 5).

In model 1, age, sex and the bed-days comorbidity score were important patient-related factors improving the model fit. Health board of residence, urban indicator, previous cancer history, and the Charlson and Scottish comorbidity indices did not improve the model fit once age, sex and bed-days had been included. Differences in age, sex and comorbidity only explained around a quarter of the deprivation-specific differences (RR reduced from 2.89 to 2.23).

Table 8.9: Patients diagnosed with melanoma in Scotland during 1997: multivariate influence of the factors grouped on the relative risk of death within two years of diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analyses)

Model Variables included in the model	Relative risk	95% CI		P-value
		Low	High	
Model 0: Null model				
Dep1: Affluent	1.00			
Dep2	1.25	0.59	2.66	0.561
Dep3	2.23	1.09	4.56	0.027
Dep4	2.04	1.01	4.14	0.047
Dep5: Deprived	2.89	1.36	6.15	<0.01
Model 1: Patient characteristics				
Dep1: Affluent	1.00			
Dep2	1.22	0.57	2.62	0.603
Dep3	2.67	1.28	5.56	<0.01
Dep4	2.01	0.98	4.10	0.055
Dep5: Deprived	2.23	1.03	4.84	0.042
Ages 15-49	1.00			
Ages 50-59	2.30	0.86	6.15	0.097
Ages 60-64	3.85	1.43	10.36	<0.01
Ages 65-69	1.70	0.50	5.74	0.396
Ages 70-74	4.49	1.65	12.19	<0.01
Ages 75-79	4.17	1.66	10.47	<0.01
Ages 80+	8.50	3.62	19.93	<0.001
Males	1.00			
Females	0.37	0.23	0.59	<0.001
No bed-days	1.00			
1-4 bed-days	0.92	0.46	1.84	0.815
5-10 bed-days	1.90	0.88	4.09	0.103
11+ bed-days	4.56	2.53	8.23	<0.001
Model 2: Health care system factors ^{1,2}				
Dep1: Affluent	1.00			
Dep2	1.41	0.65	3.07	0.380
Dep3	2.31	1.11	4.83	0.026
Dep4	2.42	1.17	5.00	0.017
Dep5: Deprived	3.25	1.48	7.13	<0.01
Low-workload consultant (<10 patients)	1.00			
Low-medium workload consultant (10-19 patients)	0.70	0.37	1.35	0.292
Medium-high workload consultant (20-25 patients)	0.81	0.40	1.62	0.549
High-workload consultant (>25 patients)	0.44	0.21	0.92	0.028
Unknown consultant workload ³	0.28	0.11	0.72	<0.01
Attended a regional RT centre	1.00			
Attended a high-workload hospital	0.56	0.33	0.96	0.034
Attended a medium-high workload hospital	0.28	0.09	0.95	0.040
Attended a medium-low workload hospital	0.56	0.24	1.33	0.190
Attended a low-workload hospital	0.29	0.09	0.98	0.046
Did not attend a hospital	1.12	0.13	9.94	0.919

¹ The wait variable was also significant but is excluded because only those not assigned a wait (i.e. the non-surgical patients) had different survival than the rest

² Age is also included in this model but the results not displayed

³ These patients have no hospital inpatient record at the time of surgery so were probably treated as outpatients

Table 8.9 continued.

Table 6/7 continued.				
Model Variables included in the model	Relative risk	95% CI		P-value
		Low	High	
Model 3: Presentation variables²				
Dep1: Affluent	1.00			
Dep2	1.27	0.59	2.74	0.544
Dep3	1.90	0.92	3.95	0.084
Dep4	1.73	0.84	3.54	0.136
Dep5: Deprived	2.12	0.97	4.64	0.059
Superficial	1.00			
Lentigo maligna	0.61	0.19	1.93	0.398
Nodular	2.82	1.33	5.99	<0.01
Acral	2.30	0.75	7.06	0.147
Other and unknown	1.37	0.76	2.46	0.290
Head, face and neck	1.00			
Trunk	0.72	0.35	1.48	0.369
Upper limb	0.50	0.19	1.28	0.147
Lower limb	0.68	0.36	1.28	0.234
Other and unknown	5.57	2.31	13.41	<0.001
Model 4: Treatment variables²				
Dep1: Affluent	1.00			
Dep2	1.05	0.48	2.33	0.902
Dep3	1.97	0.94	4.10	0.072
Dep4	1.95	0.94	4.07	0.075
Dep5: Deprived	2.69	1.24	5.85	0.012
Curative treatment intent	1.00			
Palliative treatment intent	7.22	3.65	14.28	<0.001
Unknown treatment intent	3.33	1.45	7.67	<0.01
No surgery	1.00			
Surgery	0.35	0.15	0.82	0.015
No radiotherapy	1.00			
Radiotherapy	4.10	1.79	9.41	<0.01

¹ The wait variable was also significant but is excluded because only those not assigned a wait (i.e. the non-surgical patients) had different survival than the rest

² Age is also included in this model but the results not displayed

³ These patients have no hospital inpatient record at the time of surgery so were probably treated as outpatients

Model 2 included the health care system factors, and consultant and hospital workload were important explanatory variables improving the model fit. Time from diagnosis to treatment also significantly predicted survival but was excluded from the model, because the difference was only between those with a waiting time (i.e. received surgery) and those without (i.e. no surgery), in other words measuring the fact of surgery, not time to surgery. After accounting for consultant and hospital workload, information on the specialty of the department of surgery and type of admission (routine or emergency) did not improve the model fit. After adjusting for consultant and hospital workload the gradient in relative risk of death across the deprivation groups was actually more pronounced (RR increased from 2.89 to 3.25; Table 8.9). The reason for this is not clear.

In model 3, histological type and body site were both important explanatory variables. Patients with unknown site ($n=20$) had a significantly higher relative risk of death than those with known site; if only patients with known site were considered then the risk of death between affluent and deprived patients was reduced to 1.8 ($p=0.162$; data not shown). Overall, inclusion of body site and histological type in the model reduced the relative risk of death for deprived compared to affluent patients from 2.89 to 2.12 and rendered the difference marginally non-significant ($p=0.059$).

In model 4, treatment intent (curative or palliative) was an important predictor of survival along with surgery and radiotherapy (although only 19 patients received radiotherapy). Whether the patient received chemotherapy did not influence survival after adjusting for treatment intent, surgery and radiotherapy. After adjusting for these treatment factors, the deprivation-specific difference in relative risk of death only reduced slightly from 2.89 to 2.69.

Finally, all the significant factors from the grouped models were combined in a multivariate model. After adjusting for all the factors that had a significant influence on survival from melanoma, including age, sex, bed-days comorbidity score, site of the lesion on the body, treatment intent (curative or palliative), surgery and radiotherapy, the relative risk of death in deprived compared to affluent patients was reduced by around a half from 2.89 to 1.92 (Table 8.10). The risk of death within two years of diagnosis for deprived patients was still double that of affluent patients, however the confidence interval, which contains unity, is very wide reflecting the small number of cases ($N=673$) on which the analysis was based.

In this final model, the relative risk of death decreased with increasing age, was significantly higher for women compared to men, and was decreased with increasing comorbidity as measured by the number of days spent in hospital in the preceding two years. Patients with tumours on the head, face and neck had the worst prognosis of patients with known body site. The Yorkshire audit²³⁹ found the same, and it was accounted for by tumour thickness. Patients treated with palliative or unknown treatment intent had, unsurprisingly, significantly poorer survival than those treated curatively. Patients receiving radiotherapy also had poor survival.

Table 8.10: Patients diagnosed with melanoma in Scotland during 1997: multivariate influence of all the significant variables on the relative risk of death at two years after diagnosis among deprived compared to affluent patients (Cox proportional hazards regression analysis)

Model Variables included in the model	Relative risk	95% CI		P-value
		Low	High	
Model 5: Final model				
Dep1: Affluent	1.00			
Dep2	1.06	0.47	2.39	0.885
Dep3	1.88	0.88	4.05	0.105
Dep4	1.85	0.87	3.94	0.113
Dep5: Deprived	1.92	0.86	4.31	0.112
Ages 15-49	1.00			
Ages 50-59	1.91	0.68	5.34	0.219
Ages 60-64	1.76	0.59	5.21	0.309
Ages 65-69	1.76	0.50	6.18	0.380
Ages 70-74	2.62	0.92	7.49	0.072
Ages 75-79	3.94	1.51	10.28	<0.01
Ages 80+	7.77	3.06	19.73	<0.001
Males	1.00			
Females	0.47	0.27	0.81	<0.01
No bed-days comorbidity	1.00			
1-4 bed-days comorbidity	0.75	0.35	1.57	0.440
5-10 bed-days comorbidity	2.08	0.94	4.64	0.072
11+ bed-days comorbidity	5.31	2.77	10.18	<0.001
Head, face and neck	1.00			
Trunk	0.69	0.33	1.45	0.330
Upper limb	0.40	0.15	1.04	0.059
Lower limb	0.88	0.46	1.68	0.703
Other and unknown	1.49	0.61	3.67	0.382
Curative treatment intent	1.00			
Palliative treatment intent	10.00	5.18	19.28	<0.001
Unknown treatment intent	5.08	2.25	11.50	<0.001
No radiotherapy	1.00			
Radiotherapy	3.35	1.34	8.37	0.010

Discussion

Of the cancers investigated in depth in this thesis, melanoma proved the most difficult to analyse using routine data sources. The main setback was that tumour thickness was not recorded on SOCRATES. A more minor problem was that many melanoma patients were treated as outpatients, and so for these patients there is no information about the surgical department they attended or the consultants they were seen by.

Lesion thickness is thought to be the most important factor in the prognosis of melanoma^{111,251,237}; age, sex, level of invasion and body site are also important. MacKie *et al.*²⁴⁶ found that deprived patients were more likely to present with thicker tumours in a

study of patients diagnosed in Scotland during 1979-93. They showed an increase in the proportion of thin tumours over time in all deprivation groups (affluent, intermediate and deprived), which was significant in intermediate and deprived women and affluent and intermediate men. Over 50% of all tumours were less than 1.5 mm thick, but this varied by sex and deprivation group, with only 39% of deprived men having thin tumours. The difference in tumour thickness between the deprivation groups was no longer evident in the most recent period they studied (1991-93) for females, and they speculate that a common factor, such as poor nutrition leading to low levels of antioxidants, or immunological defects, could instead be responsible for the difference in survival between deprivation groups.

In a study of patients diagnosed in Yorkshire during 1992-94, deprived patients were only slightly more likely than affluent patients to present with thicker or metastatic lesions. When lesion thickness was included in their survival model adjusting for all case mix factors (age, sex, lesion site and lesion thickness), the differences in the relative risk of death between high and low socio-economic groups they had previously identified was essentially unchanged (RR reduced from 1.25 to 1.22)²³⁹. They suggest that this was because there was no great difference in lesion thickness by socio-economic group and hypothesise that this is due to public awareness leading to early recognition and presentation across the socio-economic groups.

Public education campaigns in the mid-1980s in Scotland may have led to earlier self-referral across the deprivation groups. A questionnaire to patients presenting with melanoma in Edinburgh during the public health campaign indicated that younger patients were the most likely to have been influenced, and this age group had a higher proportion of thin tumours²³⁶.

For patients diagnosed with melanoma in Scotland in 1997, the deprived were older, were more likely to be treated as an outpatient, and to have a longer wait from diagnosis to surgery. They were also more likely to present as an emergency and to have comorbidity at diagnosis. The most affluent patients were more likely to be treated in a regional RT centre or other high-workload hospital than patients in the other deprivation groups were.

To be treated as an outpatient implies thin tumours of good prognosis, capable of being dealt with in dermatology clinics; inpatients being those in need of reconstructive surgery or

nodal dissection. However, the specialty of the department of surgery and whether the patient was seen as an inpatient or outpatient seems to be more determined by the local services available than factors relating directly to the tumour. This was also found in the Yorkshire audit. Despite the differences in melanoma services across Scotland, patients treated as outpatients did have higher survival than those treated as inpatients, implying a higher proportion of inpatients have tumours of worse prognosis, as would be expected.

There is no effective adjuvant treatment for melanoma, prompt surgery to remove the primary lesion being the only proven cure at the present time. The steeply rising incidence of melanoma, along with the much more slowly rising mortality suggests that surgical approaches to managing melanoma have improved over the past 30 years, or that melanoma is being treated earlier at a time when it is more amenable to surgical cure than was previously the case^{247,248}. If the higher survival in affluent patients is because they are presenting with thinner tumours, then the issue of lead-time bias should be considered²⁴⁶. These patients may be living longer with the disease, but their actual time of death may not have changed. However, as improvements in survival over time in Scotland are sustained at even 10 years after diagnosis¹ when the effects of this bias would be expected to be greatly reduced, the improvements in survival over time, and the gradient in survival between deprivation groups, are both likely to be real.

Another potential problem to be considered is whether the cancer registry is ascertaining all melanoma cases, particularly because some patients are not treated within the hospital setting. This problem has been identified for cancer registries in England and Wales²⁴⁹ for patients treated in the outpatient and GP setting. This means that patients with better prognosis are most likely to be missed by the registry, making survival look worse than it actually is. Due to differences in local services, this could present bias in deprivation-specific analyses. Ascertainment problems should be minimised in Scotland, however, because the registry database is frequently compared to databases independently collected by the Scottish Melanoma Group, and any missed cases are investigated.

It is interesting that consultant workload was an important determinant of survival in the multivariate model of factors relating to hospital services (Model 2; Table 8.9). The numbers of cases available for analysis, particularly for consultant workload, which could only be measured for inpatients, prevented a further breakdown of workload by specialty. It

would be interesting to look at the influence of workload within dermatology, general surgery and plastic surgery with a larger set of patients.

In conclusion, when the factors are investigated individually, differences in the relative risk of death between affluent and deprived patients appeared to be largely accounted for by comorbidity and site of the lesion on the body. When all the important factors were considered together the independent indicators of prognosis for patients with melanoma were age, sex, bed-days comorbidity score, site of the lesion on the body, treatment intent (curative or palliative) and radiotherapy. These factors explained half of the observed differences in the risk of death between affluent and deprived patients. For melanoma, only patients with late stage disease would receive treatment with palliative intent, including radiotherapy. The inclusion of these factors in the final model is, therefore, an indicator of stage of the disease. It was postulated earlier that site of the lesion on the body may also be a marker of differences in tumour thickness. Continued campaigns to promote awareness and early diagnosis should, therefore, continue and be targeted at deprived groups and particularly men.

The importance of comorbidity in the prognosis for patients with melanoma, independently of age, is also of public health significance and should be investigated further with a larger set of patients.

As well as the probable impact of tumour thickness on the factors in the final model, the remaining differences in relative risk of death between affluent and deprived patients may be accounted for by tumour thickness, although recent data from the Scottish Melanoma Group and the audit of Yorkshire patients have not identified any major differences in the distribution of tumour thickness by deprivation group. These analyses were greatly hampered because no information on tumour thickness was available.

GENERAL DISCUSSION

The main aim of this thesis was to identify the most important determinants of social variation in cancer survival in Scotland. Six cancers were identified as having significant differences in survival between deprivation groups, on the basis of the number of avoidable deaths within five years of diagnosis. The influence on the survival gradient of four types of explanatory variables: those relating to the patient, the tumour, health care system and treatment were studied. The cancers included were breast, colon, rectal, bladder and kidney cancers, and melanoma of the skin. The underlying purpose of this thesis was to investigate the use of routine data sources to look at prognosis and patterns of cancer care. The Scottish linked database of cancer registry data, hospital discharge records and deaths was utilised.

Limitations of the materials and methods that could affect interpretation of the results will be discussed first, followed by a discussion of the importance of the different explanatory variables. The potential impact of reducing avoidable deprivation-specific differences in survival is also discussed as part of the overall conclusion.

Limitations of the methods and material

Survival analyses

Cause-specific survival was not used in the analyses because of uncertainty in the accuracy of death certification and the subjectivity of the definition of "cause-specific" (see Chapter 1). In Chapter 3, the very large differences in survival estimates when using relative compared to cause-specific survival methodology were illustrated (see Table 3.7). The cause-specific estimates were generally higher than the relative survival estimates, suggesting that the differences may be due to inaccurate recording of cancer on death certificates. An alternative explanation could be an inappropriate choice of life table for the relative survival analysis. This is less plausible than inaccurate death certification because the gradients in survival across deprivation groups were similar both for the cause-specific and the relative survival analyses, whereas inappropriate life tables would be expected to have changed the deprivation gradient.

Even if cause-specific survival were accurate, competing causes of death become more important as time passes, so overall survival within two years of diagnosis should not be heavily influenced by death from competing causes. Melanoma has been used to explore the effect of adjusting for cause of death. If the analyses in chapter 8 were re-run using cause-specific deaths (and censoring non-cancer deaths) instead of all deaths, the relative risk of death for deprived compared to affluent melanoma patients would have been reduced slightly (from 2.89 to 2.27; data not shown) but it was still statistically significant.

Of the 78 patients dying within two years of diagnosis, 57 (73%) had melanoma or another related condition (see Appendix 1.1) mentioned on the death certificate and so were counted as cause-specific deaths. For 8 (13%) patients, another cancer was mentioned on the death certificate, and for five of these melanoma was the first or only registered malignancy, so arguably they, and probably all of these 8 deaths, should have been included as cause-specific deaths. The remaining 13 (17%) patients had no mention of cancer on their death certificate and this proportion varied by deprivation group. These patients were all elderly (aged 75 or older) and two-thirds had comorbidity measured by the bed-days index. Therefore, counting only the specific causes of death would probably underestimate the "true" difference in survival between affluent and deprived patients. Differences in underlying mortality between deprivation groups could probably be better adjusted for with age and comorbidity instead.

Relative survival was not a practical option for the in-depth analyses, as current multivariate relative survival methods involve generalised linear modelling where aggregated data instead of individual-level data are analysed (see Chapter 1). Because this method is based on aggregated data it is not as powerful as Cox proportional hazards regression modelling. A STATA algorithm to perform multivariate relative survival at an individual level is currently being developed (Mr A. Sloggett, personal communication).

Model checking and validation

The validity of the final Cox proportional hazards models was not discussed in the individual chapters. Initially, the survival curves for each factor and each cancer were examined to check that they did not cross or diverge considerably. In the few circumstances where the curves did cross, an attempt was made to group levels of the factor in a meaningful way.

For each cancer, the factors in the final model were assessed for proportionality using time-dependent modelling (see Chapter 1). On the whole, the factors were proportional or could be grouped to satisfy the proportionality assumption (for example, other surgery and unspecified surgery were grouped for breast cancer). However, sometimes it was not possible to perform any grouping (for example, for some factors the "unknown" group had a non-proportional hazard). In the final models, non-proportionality could not be resolved for treatment objective (breast, melanoma, bladder, kidney and colon), treatment (breast, melanoma, bladder and colon) and specialist department (kidney). There is, therefore, a small possibility of bias in the final results because of this non-proportionality. However, where factors could be grouped, the final deprivation-specific estimates were not significantly influenced by the grouping. Interaction terms were not considered, due to the added complexity of the models what would arise.

Timeliness of follow-up

In the analyses presented in Chapters 3 and 4, patients diagnosed in the most recent time period (1991-95) were only followed up until the end of 1998. This means that the five-year survival estimates were based on the three-year survival estimate for patients diagnosed 1991-95, the conditional fourth-year survival estimate for patients diagnosed 1991-94, and the conditional fifth-year survival estimate for patients diagnosed 1991-93. The overall five-year estimate may be somewhat biased, therefore, if the shape of the survival curves for patients who have already survived three or four years after diagnosis is changing significantly over time. Assuming that no such bias exists means that more timely survival estimates can be presented. Changes affecting survival in the first year after diagnosis (treatment-related, for example) are likely to be much larger than those affecting survival in years 4 and 5, conditional on already having survived 3 years, which is reasonable justification, I believe, for the approach taken.

An alternative approach which aims at even more timely detection of changes in survival is called "period monitoring"²⁵⁰. It uses more up-to-date information: for example, the one-year survival estimates for patients diagnosed during 1991-95 and followed up until 1998 would be based on patients diagnosed during 1993-98 rather than those diagnosed 1991-95, the two-year survival estimates would be based on those diagnosed 1992-97, etc. The results would then be presented as one-, three-, and five-year survival estimates for follow-up period 1998 rather than diagnosis period 1991-95. This approach was not considered in

Chapters 3 and 4 of this thesis because of the difficulties in interpreting trends in data that contain changing cohorts of patients. The timeliest data available was used for the in-depth analyses in Chapters 5-8.

The deprivation measurement

Area-based measures of deprivation applied to individuals will always result in some degree of mis-classification. From the analyses performed in Chapter 1 (see Table 1.2) we might expect at least 5% of the patients in the in-depth analyses to have been mis-classified. This means that the most deprived group will include some patients who are not so deprived and the most affluent group will include some patients who are not so affluent. This type of bias will lead to an under-estimate of the magnitude of differences in survival between the deprivation groups, and so should not affect the interpretation of the results presented in this thesis.

Quality of the inpatient discharge data

In this thesis the inpatient discharge database was utilised for information on previous diagnoses (for the Charlson and Scottish comorbidity score), time previously spent as an inpatient (bed-days comorbidity score), breast cancer operation codes, department specialties, consultant codes, and types of admission (emergency or routine).

Record linkage using probability matching, as was used to link the hospital inpatient discharge data to the cancer registry database, may produce around 4% false positive matches (wrong link) and 2% false negative matches (missed link) (see Chapter 1). For the patients analysed in this thesis, 6% of cancer patients with an hospital inpatient history did not have cancer mentioned on any of their inpatient discharge records (see Table 2.8). This means, for example, that up to 6% of patients would in fact have had comorbidity but be recorded as having no comorbidity, leading to the magnitude of real differences in survival by comorbidity group being reduced. For breast cancer operations, department specialty, consultant information and type of admission, this misclassification could lead to biased results if the probability of a mis-match varied between the deprivation groups. However, there were no differences in the proportion of patients with an inpatient history containing no mention of cancer across the deprivation groups.

For a further 5% of patients, the specific cancer recorded by the cancer registry was not mentioned on any of the inpatient records, although another or unspecific cancer code was recorded (see Table 2.8). As the cancer registry diagnosis code was used in this thesis, this will not have affected the analyses. Quality assurance of a sample of the 1996/97 inpatient discharge data found the diagnosis codes to be only 89% accurate in general (see Table 2.5), however, from the data presented in this thesis, it appears that recording of cancer diagnoses is more accurate (95%). This is useful to know for further studies which may rely on the inpatient diagnoses codes. The diagnostic and probability matching errors combined (11%) give some indication of the expected accuracy and completeness of cancer registries that register solely from electronic sources (although the availability of pathology laboratory data should reduce the diagnostic errors).

In most hospitals in Scotland, inpatient data are entered onto a patient information system. Staff record admissions, transfers and discharges with timescales as near to real-time as possible. This is sometimes achieved by ward staff having access to the systems in wards, and by departments other than medical records also having access. In other hospitals there are communication mechanisms so that all changes are notified to staff responsible for data input (usually medical records staff). Most hospitals use a combination of sources of information – admission systems, bed state reports, ward clerks, bed bureau and secretaries, and the information is collected by medical records staff, admissions clerks, ward clerks, nursing and A&E clerical staff. In addition to the staff mentioned above, clinical coding supervisors and managers hold responsibility for the completion of hospital inpatient discharge data.

Given the number of sources and people entering the data, it is not surprising that the quality has been found to be quite low for some data fields when an exercise was undertaken to re-abstract information for a 1% sample of records (see Table 2.5). However, most of the data fields used for this thesis were recorded to a very high accuracy: the date of admission and date of discharge were 99% accurate, so there should be no bias in bed-days comorbidity scores reported across the deprivation groups. Similarly, recording of specialty (100%) and type of admission (98%) were also accurate. The accuracy of the breast cancer operation codes was discussed previously and no problems were identified (see Chapter 5 discussion). The factors that could be affected by the quality of the inpatient data are the Charlson and Scottish comorbidity scores, due to the low accuracy of the diagnostic codes

(89%) and a large variability in accuracy between hospitals. These indices were only significant in the final colon cancer model, but they do show a trend of increasing relative risk of death with increasing comorbidity, as would be expected.

In summary, therefore, variations in the quality of the hospital inpatient data is very unlikely to have an important influence on the analyses presented.

Quality of the cancer registry data

In the analyses performed for this thesis, the quality of the cancer registry (SOCRATES) data is a much bigger issue. Many of the factors used in the analyses in Chapters 5-8 were collected for the first time for patients diagnosed in 1997 (see Chapter 1).

The results of reviewing re-abstracted data for a random sample of records for patients diagnosed in 1997 are shown in Table 2.4. Date of diagnosis is recorded by the cancer registration officers (CROs) and can be subjective (see Chapter 1 for definition). In the re-abstractation exercise this date varied for 25% of patients (by more than 6 weeks for 5% of patients), and may have led to bias in the "Time from diagnosis to surgery" factor, especially as the date of surgery also varied for 17% of patients receiving surgery. This factor was important for the colon and rectal cancer analyses, and results should thus be interpreted with caution.

There was a good level of agreement in the recording of tumour site (97%) and whether the tumour was histologically verified (98%). Whether or not the patient received surgery, radiotherapy, chemotherapy and hormone therapy was also accurately recorded (96-98%). Half of the discrepancies (9%) in the morphology code were in the recoding from one non-specific code to another, and most of the remaining discrepancies were in the coding of a more specific code within a general code. These differences would not have influenced the broad bandings of histological type used in this thesis.

Major discrepancies were found in the recording of clinical and pathological breast staging factors and colorectal tumour stage. These differences were mainly due to the recording versus non-recording of an informative value for the factor rather than a difference in an actual recorded informative value. The re-abstractation exercise demonstrated that the CROs had some problems in extracting this new information from the medical notes. Whether

the number of discrepancies varied significantly by hospital could not be investigated because of the large number of hospitals and relatively small sample size (461 breast records and 457 colorectal records).

If there was no bias in the distribution of unstaged cancers (i.e. all stages of cancer were equally likely to be unrecorded) then the relative risk of death for the unstaged cancers should be similar to the average risk of death for all staged cancers combined. This appears to occur for metastatic status for breast cancer, and so missing metastatic status should not bias the deprivation-specific analyses. This is further supported by the fact that imputation of metastatic status does not influence the final results.

For breast cancer, patients with no information on pathological and clinical tumour size or nodal status appeared to have a worse prognosis than the average prognosis of patients who had this information recorded. This suggests that the cancers in the unstaged group were actually more advanced. Deprived patients were more likely to have missing information. For patients with known pathological details, however, deprived patients were more likely to present with a worse distribution anyway, which may explain the worse survival in the unstaged patients. There were no differences in the distribution of the known clinical factors by deprivation group. That both clinical and pathological information were independently predictive of outcome in the final breast cancer model may be because information was not always missing for the same patients (i.e. a patient may have missing pathological size but clinical size recorded), as well as the within stage variability reported in the breast cancer chapter.

For colon and rectal cancers, patients with no information on Dukes' stage also appeared to have a worse prognosis than the average prognosis of patients who had this information recorded. Conversely, however, affluent patients were more likely to have this information missing. The implications of this were discussed in detail in Chapter 6.

Systematic variation

Bearing in mind these potential data problems, attention will now be turned to the results.

Age

Ageism is a term of the moment, and there is evidence that it existed for access and treatment among patients diagnosed in Scotland in 1997. Elderly patients were less likely than younger patients to attend a regional RT centre, and less likely to receive surgery, chemotherapy or radiotherapy for all of the cancers investigated. This was true for patients presenting with both early stage and late stage tumours, and those with no comorbidity according to the bed-days index. Of course, very elderly patients will be less suitable for treatment because of frailty and other conditions that it is not possible to measure with routine data.

Although age was an important prognostic factor for all the cancers investigated, there were no differences in the age distribution of patients across the deprivation groups, and therefore, age did not explain the differences in survival between the deprivation groups.

Sex

Females with melanoma have previously been shown to have a better prognosis than males, and this was also observed with these data: the risk of death within two-years of diagnosis was double in males than females, even after accounting for differences in the important factors including site of the lesion on the body. As there were no differences in the proportion of female patients across the deprivation groups, this factor did not explain any of the survival differences between affluent and deprived patients.

There were no differences in the proportion of males and females across the deprivation groups for the other cancers investigated with the exception of kidney cancer, and there were no differences in survival between the sexes for kidney or the other sites. Sex is therefore not an important factor in explaining the deprivation-specific differences in survival.

Place of residence

After accounting for deprivation, survival did not vary by health board of residence and urban or rural residence for any of the cancers investigated. This highlights the importance of adjusting for deprivation when looking at residential factors.

Multiple primary tumours

There were no differences between the deprivation groups in the proportion of patients who had a previous primary cancer for any of the cancers investigated. Many survival analysis studies would exclude patients who had a previous primary cancer from the analyses, however, in this study it was important to include these patients to see whether observed differences in survival were partly accounted for by a history of cancer. That this factor was not a strong predictor of outcome is encouraging for studies where different populations are compared and multiple tumours cannot be excluded (e.g. for a registry which has only been running for a short time).

Comorbidity

Improved general health status may explain some of the improvements in survival that have been observed for most cancers over time in Scotland, as the all-cause mortality rate for Scotland fell by approximately 22%, from 11.4 to 8.9 per 1 000, over the period 1971 to 1995. This reduction implies a decreasing prevalence of co-existing chronic disease in cancer patients, leading to a greater proportion of patients for whom intensive (and potentially more effective) treatment can be considered appropriate, and perhaps also to a greater resilience of patients to the side-effects of treatment.

For all the cancers investigated in this thesis, comorbidity was an important prognostic factor in the final model. This highlights the importance of comorbidity in cancer patient survival. If it had been possible to perform multivariate analysis using relative survival or reliable cause-specific death information, however, the importance of comorbidity as an independent prognostic indicator might have been reduced.

It is not possible to measure comorbidity using routine cancer registry data. For this thesis, comorbidity was measured using the hospital inpatient data, and this will tend to underestimate comorbidity both because of missed links, as discussed earlier, and because only specific illnesses of sufficient severity to result in an inpatient stay will be recorded. Comorbidity is complex and notoriously difficult to explain with a single measure, and this is highlighted in these analyses. For colon cancer patients, the two disease-based measures (Charlson and Scottish indexes) were independently predictive of survival, and the cumulative illness measure (bed-days score) did not explain extra survival variations in a model containing the two disease-based measures. For breast, rectal, bladder, kidney and

melanoma cancer patients, however, the bed-days score was a strong predictor of survival and the two disease-based measures did not explain any extra variation in the data. Clearly, any comprehensive comorbidity index will have to take into account both the impact of specific diseases and the accumulated effects of ill health.

Deprived patients had higher comorbidity than affluent patients for all the cancer investigated, with the exception of kidney cancer. As well as its impact as an independent factor in the models, insofar as measures reflect clinical comorbidity, it is likely to have influenced clinical judgement in treatment choices and referral. Factors leading to comorbidity are embedded in everyday life and are difficult but not impossible to change.

Tumour biology

Differences in the histological types of tumours between the deprivation groups were observed for breast cancer (lobular tumours were less common in deprived patients than affluent patients), and kidney cancer (clear cell tumours were less common in deprived patients). These were both histological types with a better prognosis than the other histological types, but these factors were not strong enough prognostic indicators to feature in the final multivariate models. Differences in survival between the deprivation groups were therefore not accounted for by differences in histological type.

X Deprived patients with breast cancer were more likely to have tumours with negative oestrogen receptor (ER) status than affluent patients, and ER status was an important prognostic indicator in the final breast cancer model, because prognosis is worse for women with ER-negative tumours. In a basic model containing deprivation, age and ER status, around a quarter of the differences in survival between affluent and deprived patients appeared to be accounted for by ER status (see Table 5.8). So, ER status is clearly important in explaining part of the deprivation-specific differences in breast cancer survival, but it is not something that can be altered. This is unavoidable.

Tumour grade was an important prognostic indicator for patients with breast, colon, kidney and bladder cancers. Grade was not well recorded, but deprived patients with breast cancer appeared slightly more likely to present with poorly-differentiated or undifferentiated tumours. For patients with colon, rectum, bladder or kidney cancer, there were no

differences in the distribution of grade at diagnosis. Overall, grade was not an important factor in explaining the socio-economic differences in survival for the cancers studied here.

Delay in diagnosis and tumour stage

For many forms of cancer there is a clear association between extent of disease at diagnosis and survival. Public health campaigns and public involvement in screening programmes have led to a better understanding of cancer risk and symptoms, and the potential value of early diagnosis, so trends in increasing public awareness of cancer may well have led to earlier diagnosis, independently of improvements in diagnostic techniques and screening. This could lead to an increase in deprivation-specific survival gradients if deprived patients are less likely to attend screening or to be influenced by public awareness campaigns.

Information on the extent of disease (stage) was available for breast, colon and rectal cancers, although the completeness of this information was quite low and it varied between the deprivation groups, hindering interpretation. Information on tumour thickness is not available for melanoma of the skin, and this made final interpretation of the melanoma data difficult: the factors identified as responsible for differences in survival between the deprivation groups may be independent prognostic indicators or may simply be acting as a surrogate for tumour thickness. Information on stage was not available for bladder and kidney cancer, and this again hindered interpretation of the data, because factors could not be attributed as important without the caveat that they be acting as a surrogate to stage. The difficulty in collecting stage routinely for urological cancers has been pointed out previously (see Chapter 7) and it may be necessary to gather data prospectively (on a population basis) for future studies of urological cancers.

Lack of stage information, or complete stage information, was a major drawback in the use of routine data for these analyses. Despite the problem of missing data, it was still clear that deprived patients with breast and rectal cancers were more likely to present with metastatic tumours than affluent patients, and this could account for around half the deprivation-specific differences in survival for breast cancer.

For rectal cancer patients, a combination of factors, including stage, explained almost half the deprivation-specific differences in survival in the final model. A number of these important factors would be expected to be related to stage, including type of admission,

time from diagnosis to treatment and treatment intent, and they may have been significant contributors in the final model because they, in fact, explained survival variations for patients with unknown stage. When only these factors were included in the model, along with deprivation and age, the relative risk of death was increased slightly compared to the final rectal model in Chapter 5 (from 1.41 to 1.47; data not shown), so factors relating to tumour stage seem to account for nearly half the differences in survival between deprivation groups for rectal cancer. In a data set with more complete stage information, we might speculate that about half the deprivation-specific differences for rectal cancer patients would therefore be accounted for by stage.

Health care system factors

Hospital of treatment

Notwithstanding general improvements in diagnosis and treatment over time, the organisation of cancer care is important in ensuring patients are referred to centres at which the best available cancer services can be delivered (Calman-Hine process¹⁰¹). There are five regional RT centres in Scotland, and for the patients considered in this thesis, 74% of breast, 40% of colon, 51% of rectal, 46% of bladder, 45% of kidney and 40% of melanoma patients attended one of these centres within three months of their cancer diagnosis. There is some evidence that an early effect of the breast screening programme in Scotland was to accelerate for breast cancer patients the tendency towards managed care and specialist referral which is permeating cancer services in Scotland²⁵¹. The data presented here would certainly support that, with large differences in the proportion of patients attending these RT centres by cancer and the highest proportion for breast cancer patients.

The hospital of treatment was categorised by the workload of the hospital, based on the number of patients treated with the cancer of interest over the three-year period 1996-98. The regional RT centres were included as a separate category. In the final models, the hospital of treatment was only an important prognostic factor for breast and kidney cancer patients. Breast cancer patients treated at the regional RT centres or other high-workload hospitals had a better prognosis than those treated at lower-workload hospitals even after adjusting for stage. Deprived patients with breast cancer were significantly less likely than affluent patients to be treated at a regional RT centre, and this influenced the treatments they received. Hospital of treatment was clearly an important factor in explaining the

deprivation-specific differences in breast cancer survival, whether because of treatment options available or an effect of multidisciplinary care. There was no clear trend in prognosis across the levels of hospital workload for kidney cancer, probably because of the small numbers of cases in the analysis, so no conclusions can be drawn on the importance of hospital workload for kidney cancer patients with the current data.

Specialist department

Similar proportions of patients with breast, colon, rectal and bladder cancer attended a specialist department within three months of diagnosis (80%-88%), but this proportion was lower for melanoma of the skin (73%) and kidney cancer (63%) patients. Patients with cancer of the rectum, bladder and kidney had a better prognosis if they attended a specialist department within three months of diagnosis. This will partly be explained by patients deemed fit for adjuvant radiotherapy or chemotherapy attending a specialist department, by definition. However, this factor was still significant in the models after taking account of these treatment factors. The real implication underlying the impact of attending a specialist department may be related to expertise of consultants and/or access to multidisciplinary teams.

Rectal cancer patients from all deprivation groups were equally likely to attend a specialist department, so unsurprisingly, this factor did not explain deprivation-specific differences in survival. Deprived bladder cancer patients were actually more likely to attend a specialist department, possibly reflecting their higher rates of palliative radiotherapy. Differences in survival between the deprivation groups for bladder cancer patients were increased after accounting for whether or not patients attended a specialist department due to differences for those who did not attend a specialist department. Affluent patients who did not attend a specialist department appeared to have very good prognosis tumours and deprived patients who did not attend a specialist department appeared to have a very poor prognosis.

For kidney cancer, deprived patients were less likely to attend a specialist department even though they were more likely to receive radiotherapy than affluent patients. The fact that deprived patients were less likely to attend a specialist department, either reflecting lack of access to these services or more advanced tumours, appeared to explain some of the differences in survival between affluent and deprived patients. These are factors that are to a certain extent remediable.

Managing consultant

With the routine data available, we could identify the medical code of the consultant managing the patient at time of surgery but not whether the operation was actually performed by that consultant; the consultant may not even have been present at the operation. For this reason, consultant workload may not be expected to have a strong influence on outcome. Given problems with the consultant information, no attempt was made to look at consultant expertise. The presence of a multidisciplinary team, which may actually be more important than specialism or workload, could not be measured with the data. Attendance at a specialist department was the closest surrogate available for measuring the presence of a multi-disciplinary team and specialised consultants. We might expect, therefore, for the specialist department to be a stronger factor in the models than consultant workload.

Deprived patients with breast, rectal, bladder and kidney cancer were less likely than affluent patients to be seen by a high-workload consultant. For breast cancer, increasing workload appeared to be related to better outcome initially (see Table 5.8), but after taking account of tumour characteristics this difference disappeared. For colon and rectal cancer patients, increasing consultant workload was also related to better outcome and it remained significant for colon cancer patients after adjusting for all other factors (see Table 6.9). It was surprising that it was not important for rectal cancer, where surgery is more complicated, however, specialist department was an important factor in this model. Consultant workload could not easily be measured for melanoma because so many patients were treated as outpatients.

Emergency admission does not imply that the patient had emergency surgery, just that their admission to hospital with suspected cancer was not through a routine appointment. Emergency admissions are likely to reflect worse tumour stage at presentation. For colon, rectal and bladder cancer patients, patients with an emergency admission had a poorer prognosis after adjusting for the other important prognostic factors. However, there were no differences across the deprivation groups in the proportion of patients presenting as an emergency with rectal or bladder cancer. Deprived patients with colon cancer were more likely to present as an emergency but this did not appear to impact on the deprivation-specific differences in survival.

Treatment

Treatment intent was an important prognostic factor for all the cancers investigated. It is a difficult factor to interpret because it is not often stated explicitly in the medical notes and the CROs may have to use their own judgement in recording it. One might expect it to be a surrogate of tumour stage, but for those cancers with stage information, it explained extra variability in the data on top of stage. For cancers with no stage information, it did not explain the deprivation-specific differences in survival. Although a "soft" variable, it successfully and consistently differentiated between good and poor prognosis: within a given stage, patients recorded as being treated with palliative intent always had much poorer survival than those recorded as being treated with curative intent.

Only broad categories of type of treatment were available to test the hypothesis that patients from different deprivation groups were treated unequally. However, clear differences emerged, and more detailed treatment information might have yielded even clearer results on the association between treatment and deprivation. For breast cancer, it was possible to group the types of surgical intervention into mastectomy versus breast conserving surgery, and there were large differences between deprivation groups in the proportion of women receiving each type of surgery.

Treatment is related to clinical judgement, which is related to stage at diagnosis, host factors and the setting in which you are seen. Some of the differences in treatment observed may be just, but deprived patients were consistently less likely to receive any treatment, and if they did receive treatment there were differences in the treatment combinations they received. The recorded type of treatment and the specific combination of treatment were important prognostic factors for breast, colon, kidney and bladder cancer patients, even after adjusting for the other important prognostic factors. These differences in treatment would appear not to be justified by the available data on extent of disease, and the survival differences between deprivation groups must therefore be to some extent avoidable with more equitable access to treatment.

Conclusions

Differences between deprivation groups in tumour biology, tumour stage, comorbidity, hospital and consultant, and treatments were identified for the cancers investigated. The most important determinants of the deprivation-specific differences in cancer survival for patients diagnosed in Scotland in 1997 appeared to be comorbidity, extent of disease at diagnosis, and access to and implementation of optimal treatment. As determinants of the deprivation-specific gradient in survival, the differences in tumour stage could be seen as unacceptable, differences in treatment as unjust and differences in comorbidity as unavoidable.

The routine data available provided a wealth of information and a powerful tool for identifying avoidable causes of inequalities in cancer survival in Scotland between deprivation groups. They also caused some interpretative difficulty, particularly on disease stage. This information was collected from the medical notes, so even a prospective audit study would have had similar problems unless clinicians can be encouraged to take better care at recording stage information. It is clear that reliable stage information is needed for analyses such as those undertaken in this thesis, although problems in collecting this type of information must be acknowledged.

Not all of the variation in survival between deprivation groups could be explained using the information routinely available. There may be other factors that have not been accounted for, and the lack of information on stage for bladder, kidney and melanoma patients falls into this category. The specialty of consultants performing operations, the effect of multidisciplinary teams and more detailed information on treatment regimes could also be important. Alternatively, the remaining differences that are not accounted for may be due to the crudeness of the factors used and the missing data.

Overall, the deprivation-specific differences in survival for these six cancers are most unlikely to be explained by the various limitations in the material available or the methods of analysis, with the possible exception of colon cancer, where bias from missing stage information may have hindered interpretation. Differences in underlying mortality were adjusted for using comorbidity indices. Any bias in the use of the ecological Carstairs deprivation measure will have diluted the effects of deprivation rather than enhanced them. Data quality was generally good, with the exception of stage for breast and colorectal cancer.

The overall findings for each cancer are now briefly summarised, and an estimate is given of the number of deaths that could be avoided within five years of diagnosis. These are derived from the impact (% reduction) of the adjusted risk estimates for patients diagnosed in 1997, applied to the number of avoidable deaths estimated for patients diagnosed in 1991-95 (see Chapter 4).

Between half and two-thirds of the deprivation-specific survival differences observed between affluent and deprived women with breast cancer diagnosed in 1997 can be attributed to differences in stage at diagnosis, ER status and access to optimal treatment. These differences in survival should therefore be largely avoidable by carefully targeted awareness campaigns aimed at earlier diagnosis of deprived women and more rigorous adherence by oncologists to consensus guidelines on how to treat cancer patients. If implementing such policies could realistically reduce inequalities in survival in breast cancer survival between deprivation groups by one half, some 60 breast cancer deaths within five years of diagnosis might be avoided each year in Scotland.

Around half of the difference in survival for rectal cancer patients was explained by deprived patients having worse comorbidity and stage at diagnosis, on their being more likely to present as an emergency and be treated with palliative intent (probably as a result of later stage and poor host response), and being less likely to be treated in a regional RT centre or other high-workload hospital. These differences in survival should again be largely avoidable by carefully targeted awareness campaigns aimed at deprived patients and by ensuring that rectal cancer patients attend appropriate hospitals to ensure optimal treatment. If implementing such policies could reduce inequalities in rectal cancer survival between deprivation groups by around one half, around 20 rectal cancer deaths within five years of diagnosis might be avoided each year.

For kidney cancer patients, around a third of the deprivation-specific differences were explained by differences in the treatment received. This may reflect a worse stage at diagnosis influencing the clinician judgement, but the data suggest that some of the differences are due to inequity in access to health care services. If all kidney cancer patients had equal access to multi-disciplinary teams in hospitals with the necessary facilities for optimal treatment, it seems reasonable to suggest that around one fifth of the differences in

survival should be avoidable. If this were achieved then 6 kidney cancer deaths within five years of diagnosis might be avoided each year.

Finally, deprivation-specific differences in survival for melanoma patients were explained by largely unavoidable factors including age, sex, comorbidity and site of the lesion on the body, and factors directly relating to thick tumours including palliative treatment intent and the provision of radiotherapy. Sex and site of lesion on the body may also be indirect markers of tumour thickness. The melanoma analyses were greatly hampered because no information on tumour thickness was available. If the important prognostic factors identified are truly measures of tumour thickness, then continued campaigns to promote awareness and early diagnosis, particularly in deprived men, could reduce the deprivation-specific differences in melanoma survival by one half, and some 9 melanoma deaths within five years of diagnosis might be avoided each year.

Deprivation-specific differences in colon cancer survival were increased, not reduced, by the factors investigated, after adjusting for differences in survival for patients with unstaged tumours. It is not possible to discern if this is real or a data quality artefact. For bladder cancer, none of the factors investigated explained the differences in survival, illustrating that the routine data were not sufficient. Further investigation is required, particularly with data on stage of disease.

Although this thesis has not successfully identified all the reasons for inequalities in cancer survival between deprivation groups in Scotland for the six cancers studied, it has highlighted specific areas where changes in policy would go a long way to reducing the inequalities, most importantly by enabling earlier diagnosis and ensuring that all patients have access to optimal treatment. Given the crudeness of the measures and the incompleteness of information with these routine data, it is likely that the factors identified as important actually explain more of the observed differences in survival between the deprivation groups than we have been able to illustrate.

In addressing the underlying aim of this thesis, we can conclude that it is indeed possible and useful to analyse routine data to provide meaningful and timely insights into differences in survival between deprivation groups in Scotland. Overall, to the extent that each of the

survival analyses and policy implications discussed here are plausible, then it may be suggested that almost 100 deaths from the six cancers considered here might be avoided within 5 years of diagnosis every year in Scotland. The total avoidable mortality for these cancers, if all deprivation groups had the same survival as the most affluent group, is estimated to be around 10%, and could be reduced to around 6% by reducing inequalities in stage at diagnosis and access to optimal treatment. Because of the limitations discussed relating to the available data, it is likely that removing these inequalities would actually reduce the avoidable mortality even further.

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PUBLICATIONS

A number of publications have been, or are in the process of being, written as a result of the work in this thesis:

1. The analyses in Chapter 4 were also done on English data, and published in: "Richards MA, Stockton D, Babb P, Coleman MP (2000). How many deaths have been avoided through improvements in cancer survival? *BMJ*; 320:895-8."
2. Chapter 3 was used as the basis of the summary chapter in: "Scottish Cancer Intelligence Unit (2000). Trends in Cancer Survival in Scotland 1971-1995. Edinburgh: Information and Statistics Division."
3. The following articles are in draft form and should all be submitted for publication within the next six months:
 - a. A paper describing the STATA algorithm *strel2*, which includes the analyses on the sensitivity of the algorithm and comparisons of the estimates with those provided by the *surv3* package.
 - b. A paper on the European avoidable deaths analysis: "Avoidable deaths: what if cancer survival in Great Britain was the same as in Europe?"
 - c. A paper comparing the two methods of estimating the number of avoidable deaths.
 - d. A comparison of the various comorbidity measures as prognostic indicators for cancer
4. I also intend to write papers based on the main results of Chapters 5-8.

